PhD Thesis

COPD hospitalisations in Denmark 2002 – 2009:

Factors influencing the incidence, prevalence, and lifetime risk.

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This PhD thesis has been accepted for the defence of the medical PhD by the Faculty of Health Sciences , University of Southern Denmark. The defence will be on 18 January 2013 at the Auditory, Winsløw Parken 25, DK-5000, Odense, Denmark.

Preface

The origin of this thesis

A general practitioner (GP) writing a PhD thesis on national surveillance of hospitalisations with one specific disease may seem rather strange. However, chronic obstructive pulmonary disease (COPD) is very common and in order to anticipate risks and determine when special management is required, GPs need to know what patient trajectories to expect. Also, GPs spend evermore time counselling about health risks and prevention. In doing so, the ability to predict whole lifespans of health and disease is essential to the quality of advice. Furthermore, a decision to hospitalise a patient usually involves a GP, and the severity threshold used in making such decisions concerns not only the individual patient, but also considerations regarding how the national workload of health care should be distributed across primary and secondary care. This thesis addresses all the abovementioned issues.

My particular interest in COPD began rather suddenly in June 2005. I had only recently been employed at the respiratory department of the Hospital of Southwest Jutland, Denmark, when my grandfather was admitted to another Danish hospital with signs of pneumonia. He was discharged with a diagnosis of COPD and I wondered if it was a misdiagnosis, as I considered COPD to be relatively rare among non-smokers. My grandfather had been coughing for a couple of years, but he had not been smoking in at least the 30-year period in which I had known him. One month later my grandfather was readmitted with similar symptoms and died in hospital 87 years old. My grandfather constitutes a tiny part of the data material on which this thesis is based. You will find that I was wrong to perceive his medical history as rare in any way.

In 2007 I contacted the Research Unit of General practice at the University of Southern Denmark asking for a job as a researcher. At the same time the newly established governmental Region of Southern Denmark decided that COPD should be a main focus area for healthcare improvements and a grant for one PhD student doing register-based research on COPD hospitalisations was given to the Research Unit of General practice. I accepted the challenge and the result you are now about to read.

Acknowledgements

The work was supported by a grant from the governmental Region of Southern Denmark and a research fellowship from the University of Southern Denmark.

I wish to thank my supervisors. Professor Morten Andersen taught me the trade of register-based research. Your thorough (or in your own words paranoid) way of validating and getting to know the crude register output has been an important inspiration to me. Also, our talks on how to plan and program the analyses, including many discussions on the methodological pitfalls of time-trend analysis, have been rewarding. Professor Jens Søndergaard taught me scientific writing and coached me on issues regarding COPD and general practice. You made sure that all I needed for my studies was available. All my four supervisors were involved in conceiving the ideas for the studies. Associate professor Henrik Støvring came up with the idea of focusing our studies on first-time cases and aiming for an estimate of the lifetime risk. Professor Jakob Kragstrup helped me interpret the results leading to the first paper on changes in the admission severity threshold. Even the shortest talks with you seem to find their way to the final manuscripts.

A special thank you to Statistician, PhD René dePont Christensen for his great work on the third paper about lifetime risk. Also thanks to Statistician Pia Veldt Larsen for advice on the analyses of the first paper. Thanks to my other co-authors Jesper Rømhild Davidsen (J45), MD, PhD, Maja Skov Paulsen, MD, and Thomas Bøllingtoft Knudsen, MD. Among others J45 advised me on respiratory medicine and the publishing process.

Thanks to Søren Birkeland, MD, LLM, for discussions on society and health politics. Thanks to Loni Ledderer, MPM, PhD, for discussions on philosophy of science. Thanks to Secretary Lise Keller Stark for her always skilful proofreading of manuscripts and comments on language.

I wish to thank all employees at the Research Unit of General practice. Our inspiring working environment is perhaps what assisted me the most.

Finally I wish to thank my parents and business partners in our general practice in Vejle, GPs Lise and Lars Lykkegaard, for supporting my research; and last but not least my wonderful loving wife Charlotte for helping me understand myself. To my lovely children I apologise for all the times I have been absent-minded. You are what matters most.

Jesper Lykkegaard

Abbreviations

ATC	Anatomical-therapeutic-chemical
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRS	Danish civil registration system
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HRCOPD	Chronic obstructive pulmonary disease that has required hospitalisation
ICD-10	International Classification of Diseases 10th revision
LABA	Inhaled long-acting Beta-2-agonist
NPR	Danish National Patient Registry
SABA	Inhaled short-acting Beta-2-agonist

List of papers

This PhD thesis is based on the following three papers:

I **All Danish first-time COPD hospitalisations 2002 – 2008: Incidence, outcome, patients, and care.** Lykkegaard J, Søndergaard J, Kragstrup J, Davidsen JR, Knudsen T, Andersen M. *Respir Med* 2012 Apr;106(4):549-56.

II **On the crest of a wave: Danish prevalence of hospitalisation-required COPD 2002 - 2009.** Lykkegaard J, Davidsen JR, Andersen M, Paulsen MS, Søndergaard J. *Respir Med* June 2012 [E-pub ahead of print] DOI: 10.1016/j.rmed.2012.06.004

III **Trends in the lifetime risk of hospitalisation with chronic obstructive pulmonary disease.** Lykkegaard J, Christensen RD, Davidsen JR, Støvring H, Andersen M, Søndergaard J. – *Submitted paper*

Table of contents

1 Background

1.1 The evolving understanding of COPD

Chronic obstructive pulmonary disease (COPD) is a common and preventable disease. It is characterised by persistent airflow limitation, usually progressive and associated with an enhanced inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidity contribute to the overall severity in individual patients (1). The World Health Organization ranks COPD as the fourth leading cause of death in the world (2), and in developed countries, acute exacerbation of COPD is among the most frequent causes of admission to hospital, having one of the highest inpatient mortality rates (3,4).

As in other fields of medicine, the terms and diagnostic criteria used for chronic pulmonary conditions change over time (5). Some 30 years ago the condition known today as COPD was more likely referred to as chronic bronchitis or emphysema (6). Emphysema is a pulmonary pathology (destruction of alveolar walls), while chronic bronchitis is the presence of specific symptoms (cough and sputum production). The term COPD mainly refers to the presence of persistent airflow limitation. However, in most of the patients, the triad of emphysema, chronic bronchitis, and persistent airflow limitation coexists (7). The chosen diagnosis, i.e. the term used and recorded, has depended more on time and place than on the characteristics of the patients (8). Hence, the above-mentioned three terms (and others) have been used indiscriminately to describe fairly the same group of patients.

Then, around the millennium, among international respiratory scientists a consensus gradually evolved concerning the diagnostic criteria for COPD. In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) released the report: *Global Strategy for the Diagnosis, Management, and Prevention of COPD* (9). The report emphasised the COPD diagnosis and stressed the importance of spirometry. Nevertheless, the implementation of spirometry in the daily clinic lacked behind, and even today many patients are diagnosed with and treated for COPD without the use of spirometry (10-12). This probably means that many patients with respiratory symptoms caused by other diseases, such as cardiac failure, are misdiagnosed and in error treated for COPD, while also the treatment of many true COPD patients are hampered by the lack of spirometric guidance. The spirometric criterion for airflow limitation is that forced expiratory volume in one second (FEV1) divided by forced vital capacity (FVC) must be below 0.70 (1).

As stated in the beginning of this chapter inhaled noxious particles and gases, primarily tobacco smoke, play an important role in the development of COPD. So does the susceptibility to develop the characteristic continuously enhanced inflammatory response, which disrupts the normal repair and defence mechanisms and slowly results in destruction of the parenchymal tissue and small airway fibrosis (13). These pathological changes lead to air trapping and airflow limitation, which can be measured by spirometry. The combination of chronic inflammation and pathological changes causes the characteristic symptoms: breathlessness, wheezing, coughing, and sputum production. However, the increased inflammation is not confined to the lungs. Partly, as a consequence of systemic inflammation, comorbidities such as cardiovascular disease, cancer, musculoskeletal diseases, and psychiatric disorders usually develop alongside COPD (14,15).

The destructive inflammatory pulmonary processes usually go on for decades, before fully developed COPD can be recognised (6,16-18). Hence, COPD is very rare among subjects below 40 years of age (19), and the prevalence of COPD increases with increasing age. Often the decrease in lung function is step-wise following exacerbations (20). These are acute worsening of symptoms lasting days or weeks. As the disease progresses, the frequency and severity of exacerbations usually increase (21).

In mild cases of COPD, the patients are often undiagnosed and essentially unaware of the disease, but intermittent coughing and increased sputum production may be present. In severe cases, the patients suffer from constant dyspnoea, which substantially reduces quality of life (22): Exacerbations and comorbidities often cause hospitalisations and eventually death (7). However, the process of pulmonary deterioration, development of symptoms, and loss of quality of life is so slow that patients often do not perceive it as signs of disease, but rather as normal ageing signs. Furthermore, often doctors and patients only find acute exacerbations to be isolated events of infection rather than signs of a chronic disease. Therefore, even severe cases of COPD are often undiagnosed (23,24). The undiagnosed COPD patient does not receive the medication and concern for comorbidities, which could reduce both the symptoms and the progression of the disease, as well as prolong a healthy life. More importantly, they are more likely to continue any harmful pulmonary exposure, such as smoking.

Lately it has been recognised that some patients with very severe airflow limitation live with fewer symptoms than expected and little progression of the disease. Thus, it seems that the activity of the disease

may be periodic and at times may even burn out, leaving a degree of irreversible destruction, but without further progression (25,26).

1.2 Risk factors

Given the current mean life expectancy and smoking prevalence, inhalation of noxious particles and gases (tobacco smoke) is the main risk factor for developing COPD. However, there are other inherently different risk factors, including impaired lung growth and development from gestation to adolescence (27-29), lower airway infections (27), low socioeconomic status (30), and genetically or other ways increased susceptibility to pulmonary inflammation, e.g. asthma and autoimmune disease (31-33).

It has been estimated that about 75% of COPD cases in industrialised countries is attributable to smoking, more in men and less in women (16,34); also, that more than 50% of continuous smokers develop COPD (35). However, although an abundance of different studies confirm the strong association between COPD and smoking (16,18,36), the above figures are debatable and will likely vary between populations. The near impossibility of assessing individual lifelong smoking exposures in large cohorts is one major reason, why smoking risk estimates never seem to be exact. No cohorts have been followed lifelong and also studies have usually had methodological problems with handling selection bias, confounding, loss to follow-up, and the competing risks of either development of COPD due to other causes than smoking or dying from other causes (before the development of COPD).

Investigating the population-attributable fractions of occupational exposures and outdoor air pollution the limitations are even more pronounced (34,37). Nevertheless, many studies indicate that outdoor air pollution affects lung function development and decline (34), and it has been estimated that 15-20% of all COPD cases in the US are caused by occupational exposures (38).

In the past, most studies showed that the prevalence of COPD and the ratio of all deaths caused by the disease were higher among men than women, but data from developed countries show that the prevalence of the disease is now almost equal in men and women (39,40), probably reflecting changing patterns in tobacco smoking and occupation-related exposure. Some studies suggest that women are more susceptible to the effects of tobacco smoke than men (41,42).

COPD is a disease of multicausal origin. Smoking per se, as well as all other investigated factors, is neither sufficient nor necessary to develop the disease. Further explanation of the increasing knowledge of the causes of COPD lies beyond the scope of this thesis.

1.3 Estimating the burden of COPD

Accurate estimates of the prevalence of COPD are urgently needed to anticipate the future burden, target key risk factors, and plan for providing COPD-related health services (43). In Denmark, new large so-called *super*-hospitals are to be built, but how many COPD patients should they be prepared for? Patients admitted to hospital with COPD should receive specialist treatment (3,44), but how many specialists should be trained? Rehabilitation programmes are being designed (45), but how many patients need rehabilitation? Healthcare and prevention resources are limited. How many resources should be allocated to COPD compared to other diseases and health risks? Prevalence estimates constitute a necessary basis for answering such important questions.

However, due to the process needed for collection, analysis, and publication of prevalence data, it usually takes years before actions on the results can be taken. For each year passing it becomes increasingly important to determine whether the latest reported prevalence was stable, fluctuating, or changing in any specific direction. Therefore, knowledge of the prevalence of COPD over time would be more useful than the solitary estimates usually reported. Furthermore, compared to cross-sectional prevalence studies, time-trend studies would be more useful to identify factors influencing the prevalence; especially if the prevalence of factors with suspected influence was investigated along with the prevalence of the disease.

In Western Europe and North America, among adults aged 45 years and above, the prevalence of severe COPD is 1-2%, while the prevalence of any stage COPD is about 10% (24,40,43,46-50).

Trend studies of COPD prevalence are few. Repeated cross-sectional surveys from Finland and Spain, and a Canadian cohort study of healthcare claims, indicate that the above levels of COPD prevalence are constant or maybe decreasing (51-53). Danish data from death certificates during the past decade show an almost constant rate of deaths caused by COPD (54). However, data from the World Health Organization (WHO) for all of Western Europe show an increase from 3.1 to 3.3% when comparing year 2004 to 2008 (55).

COPD prevalence is usually estimated from population surveys, in which the identification of COPD

is based on either spirometry verified airflow limitation, reported symptoms, or patient-reported doctor diagnosis of COPD (56). However, many patients with symptoms of bronchitis do not present with airflow limitation and many patients with airflow limitation do not report a doctor's diagnosis of COPD (46, 52). Hence, COPD prevalence data differ remarkably due to survey methods, diagnostic criteria, and analytical approaches. This makes prevalence comparisons between populations and over time difficult to interpret (19).

Among patients with COPD, admission to hospital indicates more symptoms and results in higher levels of costs; not to mention severely reduced quality of life (3,57-60). Also, patients who have been hospitalised with COPD have more exacerbations and more comorbidity. Furthermore, regardless of lung function impairment COPD hospitalisation dramatically increases mortality (61). Therefore the COPD hospitalisation rate is a valuable indicator of the burden of the disease. Another indicator would be the prevalence of subjects who have been hospitalised with COPD. In this thesis they are referred to as having hospitalisation-required COPD (HRCOPD). According to the above they deserve a special status among patients with COPD. Nevertheless, the prevalence of HRCOPD is not reported in the literature.

In Denmark, all COPD hospitalisations are to public hospitals. Administratively used records of all hospitalisations and diagnoses are kept in national registers. Studies have found the recorded hospitalisation diagnoses of COPD highly valid and much more reliable than COPD diagnoses recorded on death certificates (10,62). Hence, considering the completeness and validity of the records, compared to trend estimates based on either death certificates or repeated prevalence surveys, changes in the rate of register-recorded COPD hospitalisations may more accurately reflect changes in the total burden of the disease. Time-trends in COPD hospitalisation rates have been reported in several developed countries. The rate of COPD hospitalisations in France has recently been increasing (63), while in Denmark, Finland, and the US, COPD hospitalisation rates ceased to increase around the millennium, after which they seem to be decreasing (39,64-71). Also, in Brazil, Ireland, and Australia recent COPD hospitalisation rates are decreasing (72-75). In most of the above-mentioned countries COPD hospitalisation rates for women have caught up with and are now exceeding the rates for men. Changing smoking patterns is the most likely explanation for this development, but in the next chapter and later on in this thesis many other factors influencing the crude rate of COPD hospitalisations are discussed.

Since COPD is a progressive disease, incidence, prevalence, and hospitalisation rates increase with

increasing age. However, the few studies specifically reporting rates among the oldest old, i.e. above 85 years of age, consistently show that above a certain age the rate of COPD actually decreases with increasing age (65,76). The reasons for this finding have not been explained.

Although the COPD epidemic seems to have reached a maximum in developed countries (5), the worldwide burden of the disease is still expected to increase (56).

1.4 Factors influencing COPD hospitalisation rates

1.4.1 General considerations

The total number of COPD hospitalisations in a population in a given time period depends on the age- and sex-specific rates of COPD hospitalisations in the population and the number of subjects in each age- and sex-specific stratum. The number of subjects in each stratum depends on birth cohort numbers, migrations, and mortality. Especially in the elderly, the overall mortality is related to the COPD prevalence and the COPD-specific mortality. This means that decreasing mortality from COPD increases the number of elderly subjects, which might in return actually cause the number of COPD hospitalisations to increase. Similar considerations are why, all things being equal, ageing of the population leads to more COPD hospitalisations (1,77).

The age- and sex-specific rates of COPD hospitalisations depend on the rate and severity of exacerbations and the average severity threshold for admission to hospital. The rate of exacerbations in the population depends on the average frequency of exacerbations in individuals. Readmissions are frequent. Therefore the total number of hospitalisations is sensitive to how often one exacerbation leads to more than one recorded hospitalisation. This depends on the character spectrum for exacerbations, the average thresholds for admission and discharge, and the recording procedures regarding COPD hospitalisations. Last but not least, the age-specific rates and severity of COPD exacerbations depend on the population's historical and present exposures to risk factors and the extent of effective COPD treatment.

1.4.2 Incidence, prevalence, and lifetime risk

Due to the above considerations, surveillance of crude COPD hospitalisation rates, as those reported in the previous chapter, provides dubious information on what is actually changing. Discrimination is lacking

between changes in the incidence of severe COPD exacerbations, the prevalence of subjects who have the exacerbations, the risk of readmission, the average severity threshold for admission and discharge, and the mortality of subjects with and without COPD.

The age- and sex-specific incidence rates of first-time hospitalisations and the prevalence of subjects with HRCOPD provide a much clearer picture. However, the full spectrum of age-specific incidence rates is difficult to communicate to patients and politicians. Also, it expresses the burden of disease in a way that is difficult to compare across time, countries, and diseases. Furthermore, the incidence rate of (risk of developing) a chronic disease at some future age provides little information to a patient, if the chances of surviving until that age without already having developed the disease are not considered.

A lifetime risk estimate represents a way of overcoming the above-mentioned downsides of age-specific incidence rates. It sums up the spectrum of age-specific incidence rates and rates of disease-free survival into one single figure, which is more readily communicated and compared (78-80). Although such estimates are commonly used benchmarks with regard to other chronic diseases, such as cardiovascular disease and cancer, they have not until recently been adopted in COPD (50,76,80-83).

1.4.3 Risk factors

In a population, the most important determinants of the future incidence of COPD exacerbations are the prevalence and amount of smoking. However, usually, people start smoking when they are young, but they do not develop COPD until around the age of 60 years (18). Hence, for an average smoker it takes at least 30 years of smoking to develop COPD.

In the decade following World War Two, the consumption of tobacco reached a maximum in large parts of the developed world (84,85). In Denmark, the height of tobacco consumption lasted from 1950 to 1972, after which the consumption has been gradually and substantially decreasing (86). The recent decreases in COPD hospitalisations in developed countries may be the long waited result of decreases in smoking over the past 40 to 50 years, which has already caused the incidence of lung cancer to decrease (84).

Other important long-term cumulated exposures include occupational airway exposures and outdoor air pollution (34). In developed countries, the highest prevalence of those risk factors was almost in the same

historical period as the peak of the smoking epidemic. At population level, this makes distinction between smoking, occupational exposures, and outdoor air pollution as causes of COPD very difficult.

Contemporary population exposures are also important determinants of the present rate of COPD exacerbations. They primarily include seasonal changes in weather conditions and epidemic infections (87), while the short-term effects of smoking, occupational exposures, and outdoor air pollution are unclear. For example, the individual rate of severe exacerbations does not significantly decrease until 5-10 years after smoking cessation (88). However, in Massachusetts, USA, COPD hospitalisation rates decreased shortly after the implementation of a large-scale smoking cessation campaign (68).

Socioeconomic conditions are also considered important to the development and progression of COPD. The mechanisms of this effect are unknown, also whether it is a temporary or long-term effect (30).

1.4.4 Treatment

In both individuals and populations, effective management and prevention can significantly reduce the number of severe COPD exacerbations. Non-pharmacological interventions include stopping any harmful exposures, physical exercise (89), and a diet preventing both obesity and underweight (90). The substantial population-level effects of these preventive interventions are indisputable, although difficult to quantify.

In general, the pharmacological treatment of COPD has little effect on the progression of the disease (1). However, among 40- to 80-year-old patients with COPD, who have at least a 10-pack-year history of smoking and a prebronchodilator FEV1 of less than 60% of the predicted value, inhaled longacting-Beta2-agonists (LABA) such as Salmeterol induce a reduction of nearly 20% in the need for hospitalisation with acute exacerbation of COPD (91). Furthermore, compared to Salmeterol the inhaled anticholinerg, Tiotropium, which was introduced in Denmark in 2002, has proven even more effective in reducing hospitalisations (92). In severe COPD, LABA are often administered in fixed dose combinations with corticosteroids, but the additive effect of inhaled corticosteroids is small (91). Intravenous or oral treatment with corticosteroids during exacerbations reduces recovery time, the risk of early relapse, and the length of stay in case of hospitalisation (93,94). Moreover, treatment with corticosteroids early in the exacerbation period further improves their effect (95). Therefore, though investigations are lacking, it is likely that early treatment with corticosteroids in cases of exacerbation would reduce the need for hospitalisations. Hence, although pharmacological treatment does not cure COPD, if the right patients took the right drugs at the right

time probably the hospitalisation rate could be considerably reduced.

Other therapeutic options assumed to have a population-level effect on exacerbations include pneumococcal and influenza vaccinations. Also novel drugs such as phosphodiesterase-4 inhibitors may have an effect (96).

Often COPD exacerbations as well as the daily symptoms associated with COPD are aggravated or even caused by comorbidities. Cardiovascular diseases such as myocardial infarction, cardiac failure, and pulmonary embolisms are often found in patients hospitalised with COPD, and in autopsies of patients believed to have died from COPD they are often the true cause of death (97-100). Thus, most likely, the increased effective pharmacological treatment and prevention of cardiovascular disease have had a large positive population-level impact on the quality of life, survival, and need for hospitalisations among patients with COPD. This effect is, however, difficult to measure. Other comorbidities having a substantial influence on the patients' wellbeing and need for healthcare resources include cancer (15), osteoporosis (101), and psychiatric disorders such as depression and anxiety (102,103). The burden of COPD has probably also benefited from the medical improvements within these fields.

1.4.5 The admission severity threshold

Whether a patient with exacerbation of COPD is admitted to hospital depends on the severity of the exacerbation and the severity threshold for admission to hospital. For simplification, in this thesis the admission severity threshold is referred to as an unambiguous entity. This is rather crude, because in each case the threshold and the factors determining it are different. In general, the better the means of keeping the patient outside hospital, the less likely the patient is to be admitted to hospital. Among others, those means include the resources of near relatives, the home care facilities (104), and the availability and abilities of the GP (105-107). Also, the availability of hospital admission plays a role. If the hospital department has no available beds and is located far away, the patient is less likely to be admitted. The decision to admit involves many persons and individual considerations. Mainly the patient and the GP, but also relatives, hospital doctors, and sometimes care assistants or other parties take active part in the decision on whether a patient with COPD exacerbation should be hospitalised.

Within research on various diseases hospitalisation is usually considered a hard endpoint. Hence, in contrast to the above considerations, the admission severity threshold is assumed to be constant and equal for all cases. However, both assumptions are unlikely to be fulfilled.

In the past decade, the European healthcare infrastructure has been increasingly specialised into fewer units with larger patient volumes. This means that many patients must travel further to be hospitalised, while at the same time the number of acute care beds are being reduced (108). In Denmark, the total number of beds in departments of internal medicine decreased from 6970 in January 2002 to 6087 in December 2008, a decrease of 13% (109). Such changes may have increased the average severity threshold of COPD hospitalisation in Denmark and in other countries that have experienced similar trends within secondary healthcare. Furthermore, regarding COPD, studies suggest that the treatment in Danish primary care is improving (110,111). This may have reduced the frequency of severe exacerbations. However, regardless of that, more capable and confident GPs are less susceptible to hospitalise the patients. Hence, improvement in primary care increases the average admission severity threshold. This may also be an international trend.

The above considerations may apply to large parts of the developed world and to diseases other than COPD. Nevertheless, changes over time in the average admission severity threshold have rarely been investigated.

2 Background at a glance

- COPD is among the most important health problems in the developed world and hospitalisations constitute a useful marker of the burden of the disease.
- Ageing populations tend to increase this burden, although hopes are that decades of decreasing tobacco consumption will finally have an impact.
- In the developed world, studies indicate that the crude rate of COPD hospitalisations has reached a maximum. However, the extent and direction of change are still unclear. Prior trend studies have neither investigated the incidence of first-time COPD hospitalised subjects nor the prevalence of subjects with HRCOPD. Thus changing readmission and mortality rates may bias their estimates.
- Improvements in primary care, centralisation into fewer but larger hospitals, and the continuous reduction in hospital beds may cause the rate of hospitalisations to decrease. This would be a consequence of increases in the average admission severity threshold as opposed to an indication of decrease in the incidence of the disease. In order to discriminate between the two mechanisms of change, trend studies of COPD hospitalisations should include indicators of case severity.
- The whole spectrum of age-specific incidence rates of first-time COPD hospitalisations is hard to communicate and difficult to compare across time, countries, and diseases. Furthermore, without the complementary rates of disease free survival, it provides little information. The estimation of a lifetime risk combines the two spectres of age-specific rates into one single figure, which is easier to communicate and compare.

3 Aims of thesis

The aims of the present studies were:

I. To investigate trends in first-time hospitalisations with chronic obstructive pulmonary disease in a publicly financed healthcare system during the period from 2002 to 2008 with respect to incidence, outcome and characteristics of hospitalisations, departments, and patients.

II. To investigate age- and sex-specific trends in the prevalence of hospitalisation required COPD in Denmark from 2002 to 2009.

III. To estimate the lifetime risk of hospitalisation with chronic obstructive pulmonary disease.

4 Methods and materials

4.1 Design

We conducted a register-based time trend analysis covering the entire Danish population (5.43 million in 2008 (112)) from 1994 to 2009.

4.2 Setting and data sources

In Denmark, admission to public hospitals is free of charge and with equal access for all citizens. All admissions with COPD are to public hospitals and occur either by referral from a general practitioner or in severe cases as direct emergency admissions.

Since 1977, the Danish National Patient Registry (NPR) has recorded administrative data from all Danish admissions to hospital (10). From 1994 and onwards, diagnoses are classified according to the International Classification of Diseases 10th revision (ICD-10). All data are registered with the patients' unique civil registration number, which allows data linkage on an individual level between all national registers (113).

During the study period we identified all hospitalisations with COPD in Denmark and linked the individual health administrative data with data from the Demographic Register regarding the patients' dates of birth, death, and migrations to or from Denmark. For the years 2002 to 2009, the Demographic Register also provided age- and sex-specific numbers of subjects and deaths in the total Danish population.

4.3 Definition of COPD hospitalisation

COPD hospitalisation was defined as any hospitalisation with either ICD-10 codes J41-44 (COPD, chronic bronchitis, or emphysema) as primary diagnosis or with J13-18 (pneumonia) or J96 (respiratory failure) as primary diagnosis combined with either of J41-44 as a secondary diagnosis. This definition was partly adopted from the Danish National Indicator Project (114) on COPD under the Danish National Board of Health. However, in order to increase the sensitivity of the definition the codes J40-43 were included. For general population studies of prevalence and incidence, a later published validation study on the COPD diagnosis codes in the NPR recommended this expansion of the definition (10). In order to show the

implications of this expansion, separate analyses of hospitalisations coded with J40-43 and J44 were carried out.

In the incidence and prevalence studies (I and II) only patients above 45 years of age were included. The rationale behind this restriction was to reduce the potential inclusion of patients with asthma misclassified as COPD and to use the same criteria as the, at that time, most recently published Danish COPD prevalence study (40), and also to follow the way of reporting of a large Danish national report on COPD (64). In the lifetime risk study (III), the criterion was expanded to include patients above 30 years of age. This was the same age limit as the above-mentioned validation study (10), and we wanted to include as much as possible of the entire lifespan while still minimizing misclassification.

4.4 Definition of incident and prevalent cases

Between January 1 1994 and January 1 2009 all Danish COPD hospitalised subjects and dates of each subject's COPD hospitalisations were identified. First-time COPD hospitalisations (incident cases) were defined as any COPD hospitalisation of a subject who had not been hospitalised with COPD within a period of 8 years before the hospitalisation in question. Correspondingly, subjects were classified as prevalent with HRCOPD between first COPD hospitalisation and death, migration, or the end of 8 years of individual follow-up with no COPD hospitalisations (whichever occurred first). The 7-year study period and the longer 8-year look-back period were chosen because ICD-10 classified data were only available from year 1994 to 2008 and we wanted both unbiased trend estimates and to avoid the possibility of the same subject being regarded as first-time hospitalised twice in our study period. In order to determine whether extension of the look-back period would change our results we analysed the lifetime risk in year 2008 with both 8 and 14 years look-back periods. Furthermore, all subjects who had more than 8 years of COPD hospitalisation-free survival following their first COPD hospitalisation were identified.

4.5 Estimation of lifetime risk

Each 1 January from year 2002 to 2008, all Danish subjects aged above 30 years were categorised as being either prevalent with or at risk of HRCOPD. For each calendar year, all subjects at risk in the beginning of the year were further categorised as having either died or been hospitalised with COPD (whichever occurred

first), or as remaining at risk throughout the year. Using one-year age strata from age 30 years until >99 years, the age- and sex-specific numbers of subjects in each category were calculated for each calendar year. The incidence rates of first-time COPD hospitalisations and the mortality rates of subjects never hospitalised with COPD were estimated from the number of incident subjects and the number of subjects who died before COPD hospitalisation, respectively, divided by the number of subjects at risk in the beginning of each year.

A method described by Keiding was used to estimate the lifetime risk of COPD hospitalisation (78). Briefly, in order to calculate the risk of experiencing a hospitalisation with COPD for the first time at a given age, the method combines the incidence rate at that age with the probability of disease free survival until that age. When integrated over the entire age range this yields the lifetime risk. The disease-free survival probability can be computed directly from age-specific rates of incidence and mortality. Confidence intervals were calculated using bootstrap techniques.

4.6 Analyses on mortality

From January 1 1994 to December 31 2009, all deaths of subjects with HRCOPD were identified. Deaths were considered as inpatient if they occurred before the final hospital discharge date, including deaths after one or multiple transfers between hospitals and departments. Among the first-time COPD hospitalised patients, inpatient and one-year mortality proportions were calculated. Also, for each year, in each age- and sex-specific strata of the HRCOPD prevalent population, by dividing the number of deaths by the sum of prevalent subjects by 1 January and the incident subjects of the year in question, the mortality rate of subjects prevalent with HRCOPD was estimated. For each year, dividing the total number of deaths in the Danish population minus the deaths in the HRCOPD population by the total Danish population minus the sum of the prevalent and incident subjects of the year in question equalled the annual mortality rates of the population without HRCOPD.

$$Mortality\ rate\ with\ HRCOPD = \frac{Deaths\ among\ patients\ with\ HRCOPD}{HRCOPD\ prevalence\ 1\ januar + incidence\ of\ the\ year}$$

$$Mortality\ rate\ without\ HRCOPD = \frac{Total\ deaths\ in\ Denmark - Deaths\ among\ patients\ with\ HRCOPD}{Total\ population\ in\ Denmark - (HRCOPD\ prevalence\ 1\ januar + \ incidence\ of\ the\ year)}$$

4.7 Data on patients, hospitalisations, and care

From the Danish National Board of Health we annually retrieved names, addresses, medical specialities, and bed occupancy rates for all Danish hospital departments during the study period. We linked these data with the patient-specific data by use of admission year and department identification codes. Using the patients' civil registration numbers and dates of first-time COPD hospitalisations we retrieved the following register data on the patients:

The Demographic Register provided home addresses of the patients in the year of hospitalisation, so that travel distance between the patients' homes and the receiving hospitals could be calculated. In case the hospital and department codes did not sufficiently specify the location of admission, the location with the shortest travel distance was chosen. The uncertainty as to the location of an admission would be a result of hospital mergers, in which recording practices were merged months or years before the planned closing of one of the involved hospitals. Changes in the residence of a citizen are often recorded with a delay. Therefore, records of residence were obtained on 1 January before and after the COPD admission date. If the calculated travel distance differed between the two January dates, the mean of the two distances was used. However, HRCOPD patients are usually old and hence only few change their residence.

The Danish National Prescription Registry comprises information on every medical product sold on prescription in Danish pharmacies since 1994 (115). It provided dates and anatomical therapeutic chemical (ATC) codes on each drug sold to every patient.

The Primary Health Care Database comprises individually linked information on every service provided by Danish GPs since 1990. For each patient, it provided dates and service codes regarding all encounters in general practice. More than 98% of the Danish population is listed with a specific practice in which chronic diseases such as COPD are to be managed (116). The database specifically identifies encounters in the patient's listed practice and except for out-of-hours home visits this study only includes GP encounters in the listed practice.

4.8 Generated variables

Patients are often transferred between hospitals and departments. In case of transfer a record of a new hospitalisation is made in the NPR. Such transfers include transfers from the emergency/receiving

department, to and from an intensive unit, as well as COPD comorbidity-related transfers. Therefore, it was chosen to merge these hospitalisations, so that length of stay was measured from the first admission to the last discharge. However, department specialty, bed occupation rate, and patient travel distance were based on the department in which the COPD diagnosis was made.

For each annual cohort of first-time hospitalised COPD patients we calculated the average length of stay, the proportion of hospitalisations with stay on a ward classified as an intensive care unit, the proportion of hospitalisations more than 25 km from the patient's home address, the average Charlson comorbidity index (excluding COPD), and the average number of prior all-cause hospitalisations. The latter two were based on every patient's individual 8-year periods prior to their first COPD hospitalisation. The Charlson index was calculated by means of ICD-10 coded diagnoses from all in- and outpatient admissions (117). For one year prior to the patients' first COPD hospitalisation we calculated the patients' average number of encounters in general practice, and the proportions of patients having had spirometry in primary care, outpatient hospital treatment for COPD, and prescriptions of inhaled COPD medication and oral steroids, respectively. Finally, based on the report from each patient's receiving department in the year of hospitalisation, we calculated average annual bed occupancy rates.

4.9 Statistics of the time-trend analyses

By use of direct age- and sex-standardisation to the Danish 2009 population, the 2002 and 2009 COPD prevalence proportions were compared. Likewise, the 2002 and 2008 incidence rates of first-time COPD hospitalisations were compared with standardisation to the Danish 2008 population.

By means of age- and sex-adjusted logistic and Poisson regressions, both with calendar year as the primary independent variable, trends in the prevalence of HRCOPD and in the incidence rates of first-time COPD hospitalisations were estimated. Trends in mortality and all the above-mentioned characteristics were estimated by means of either logistic regression models or linear regression models. Bootstrap estimations were used in the linear models due to variance heterogeneity of the residuals. All models were adjusted for age and sex, and both the annual change and the total change from 2002 to 2008 and 2009, respectively, were investigated. Coefficient plots and likelihood tests of fractional polynomials confirmed that it was reasonable to use year as a continuous variable without transformation. All analyses were performed using STATA Release 10.1 (STATACorp, College Station, TX, USA).

4.10 Ethics

The study was approved by the Danish Data Protection Agency (No. 2009-41-3337). As the study was register-based, according to Danish legislation no approval from the Biomedical Research Ethics Committee was required. Data were made available for further analysis with an anonymised but unique person identifier, so that subjects could not be identified.

5 Results

In Denmark, during the period from 2002 to 2008 a total of 47 728 subjects aged 45 years and above were hospitalised 161 993 times with COPD. More than 99.9% of the hospitalisations took place in public hospitals and 96% were admissions to departments of internal medicine. The number of hospitals receiving COPD patients decreased from 70 to 58 over the period.

The overall annual rate of COPD hospitalisations decreased from 460 to 410 per 100 000 person years.

5.1 Incidence and prevalence of HRCOPD

In Denmark, annually about 7000 subjects aged 45 years and above are admitted to hospital for the first time with COPD. In January 2009, about 33 000 Danish subjects had at some point been hospitalised with COPD (Table 1).

During the period from 2002 to 2008, among subjects aged 45 years and above, the corresponding age- and sex-standardised incidence rate of first-time COPD hospitalisations decreased from 330 to 300 per 100 000 person years. The age- and sex-adjusted incidence rate ratio between 2008 and 2002 was 0.92 (95% CI 0.89-0.95), and analysing data for all the years, the adjusted decrease in the incidence of first-time hospitalisations was 1.2% per year (95% CI 0.8-1.7%) (Table 2). Monthly incidence rates showed a large seasonal variation (Figure 1).

The decrease in the incidence of first-time COPD hospitalisations was predominantly among males aged 60 to 79 years. In contrast, there were significant increases in the incidence among females aged 80

years and older (Table 2). Throughout the period, the 46% proportion of male first-time COPD hospitalised subjects remained constant, while the average age increased from 71.6 to 72.2 years (Table 3).

In January 2009, an overall HRCOPD prevalence proportion of 1.36% was found. For males the age-specific prevalences were: 45-59 years 0.36%, 60-74 years 1.37%, 75-84 years 4.13%, 85+ years 4.33%, and for females: 45-59 years 0.49%, 60-74 years 1.74%, 75-84 years 3.96%, 85+ years 2.99% (Table 4). In 2009, the prevalence of HRCOPD increased with age until the age of around 90 years for males and 80 years for females, after which it decreased with increasing age. Seven years before, in 2002, in both sexes the prevalences peaked at ages about 7 years earlier. A similar pattern was observed in the age- and sex-specific incidence rates of HRCOPD, while the mortality of subjects with HRCOPD increased with increasing age throughout life (Figure 2).

During the period from year 2002 to 2009, the overall prevalence of HRCOPD remained constant. However, with respect to age and sex highly significant trends were uncovered (Figure 3 & Table 4). The prevalence gradually decreased among males and subjects aged below 75 years, while it increased in the age groups above 75 years and among females. The most extreme changes were the prevalence among females aged 60 – 74 years decreasing 20%, while among females aged above 85 years increasing 36%. For males aged 60 - 74 years it decreased 25% while it increased 12% in the age group above 85 years of age. The overall prevalence among females increasingly exceeded the one of males both in absolute and relative numbers (Table 3).

5.2 Mortality

In 2008, the inpatient all-cause mortality of patients first-time hospitalised with COPD was 7%, while 25% of the patients died within one year. During the study period, in both mortality measures, significant age- and sex-adjusted increases were observed. Both inpatient and one-year age-adjusted mortality were higher in males than in females. The increase in inpatient mortality was predominantly among males, while the increase in one-year mortality was equal among the sexes (Table 3).

In 2008, among subjects aged 45 years and above who were prevalent with HRCOPD, the mortality rate was about 14% per year (Table 1). During the period from 2002 to 2008, the age- and sex-adjusted mortality decreased: OR 0.981 per year (CI 0.976-0.987). However, among subjects without HRCOPD the adjusted contemporary relative decrease was even higher: OR 0.976 per year (CI 0.974-0.976).

5.3 Patients, hospitalisations, and care

Regarding first-time COPD hospitalisations during the period from 2002 to 2008, the study uncovered substantial age- and sex-adjusted trends in the characteristics of patients, hospitalisations, and care. The use of intensive care units increased. So did the comorbidity of the patients both in terms of the Charlson index and the number of all-cause prior hospital admissions. The patients' prior diagnoses with cardiovascular disease, diabetes, cancer, and other diseases all increased substantially and gradually throughout the period.

The proportion of patients who travelled beyond 25 kilometres to hospital more than doubled, while the average bed occupation rate of the receiving departments increased beyond fully occupied. Meanwhile the average length of stays decreased.

With respect to the year prior to the first COPD hospitalisation the proportion of patients treated in outpatient hospital clinics for COPD increased. Further, the proportion of patients who had a spirometry in primary care and the frequency of primary care encounters also increased, except for daytime home visits which became fewer, while home visits after hours remained constant. Regarding the respective proportions of patients who had redeemed at least one prescription for either inhaled long-acting beta-2 agonists (LABA), tiotropium, or corticosteroids (oral as well as inhaled) in the year prior to admission, substantial increases were observed. Meanwhile, the proportion of patients who had redeemed a prescription for inhaled short-acting bronchodilators (beta2agonists or anticholinergics) decreased.

All the above trends were gradual over the period and not just the result of cross-sectional comparisons between the years 2002 and 2008 (Tables 2 and 3).

5.4 Lifetime risk

During the period from year 2002 to 2008, for first-time hospitalisation with COPD at an age above 30 years a cumulated person risk time of 23.9 million person years was observed. We identified 22 749 males with first-time COPD hospitalisations and 26 210 females.

During this period, in both sexes, the residual lifetime risk for 30-year-olds to be admitted to hospital with COPD hospitalisation remained roughly constant (Table 5). Therefore, no further trend analyses were

made. Based on the total period, the lifetime risk was 12.0% (95% CI 11.9-12.2) for females and 10.9% (95% CI 10.8-11.1) for males.

For females, from 30 to 99 years of age, the residual lifetime risk continuously decreased with increasing age. For males the residual lifetime risk increased slightly from the age of 30 until about 50 years of age, after which it decreased. At 30 years the risk was higher in females, but above the age of about 65 years it was higher in males (Figure 4, Table 6).

5.5 COPD diagnosis codes

The proportion of first-time hospitalisations with ICD-10 codes J41-43 (chronic bronchitis or emphysema), as opposed to J44 (COPD), decreased from 10.8% in 2002 to 6.7% in 2008. In absolute numbers, this decrease alone was more than the total decrease in first-time COPD hospitalisations (Table 4).

Based on the 2002 first-time hospitalisations, comparing patients coded with J44 to those with J41-43, the mean age, gender, mortality, comorbidity, use of intensive care, and encounters in general practice did not differ. However, patients coded with J41-43 were less often treated with inhalation drugs and less often treated for COPD in outpatient clinics than those coded with J44. They were admitted to less crowded departments, which were less often specialised in internal medicine and to which they had to travel a bit further.

In contrast to the observed similarities between patients coded with J44 and J41-43, patients coded with J13-18 (pneumonia) or J96 (respiratory failure) had a much higher mortality, comorbidity, and use of intensive care units than patients coded with J44 or J41-43 (Table 7).

5.6 Regarding the 8-year look-back period

In year 2008, among the 33 031 subjects prevalent with HRCOPD 1315 left the prevalent cohort because in 8 years they had not been hospitalised with COPD (Table 1).

Regarding our lifetime risk calculations, extending the look-back period for the analysis of year 2008 from 8 to 14 years did not lower the estimates substantially: Males from 10.7% (95% CI 9.8 – 11.7) to 10.5% (95% CI 10.0 – 11.1); Females from 12.3% (95% CI 11.3 – 13.3) to 12.0% (95% CI 11.2 – 12.7).

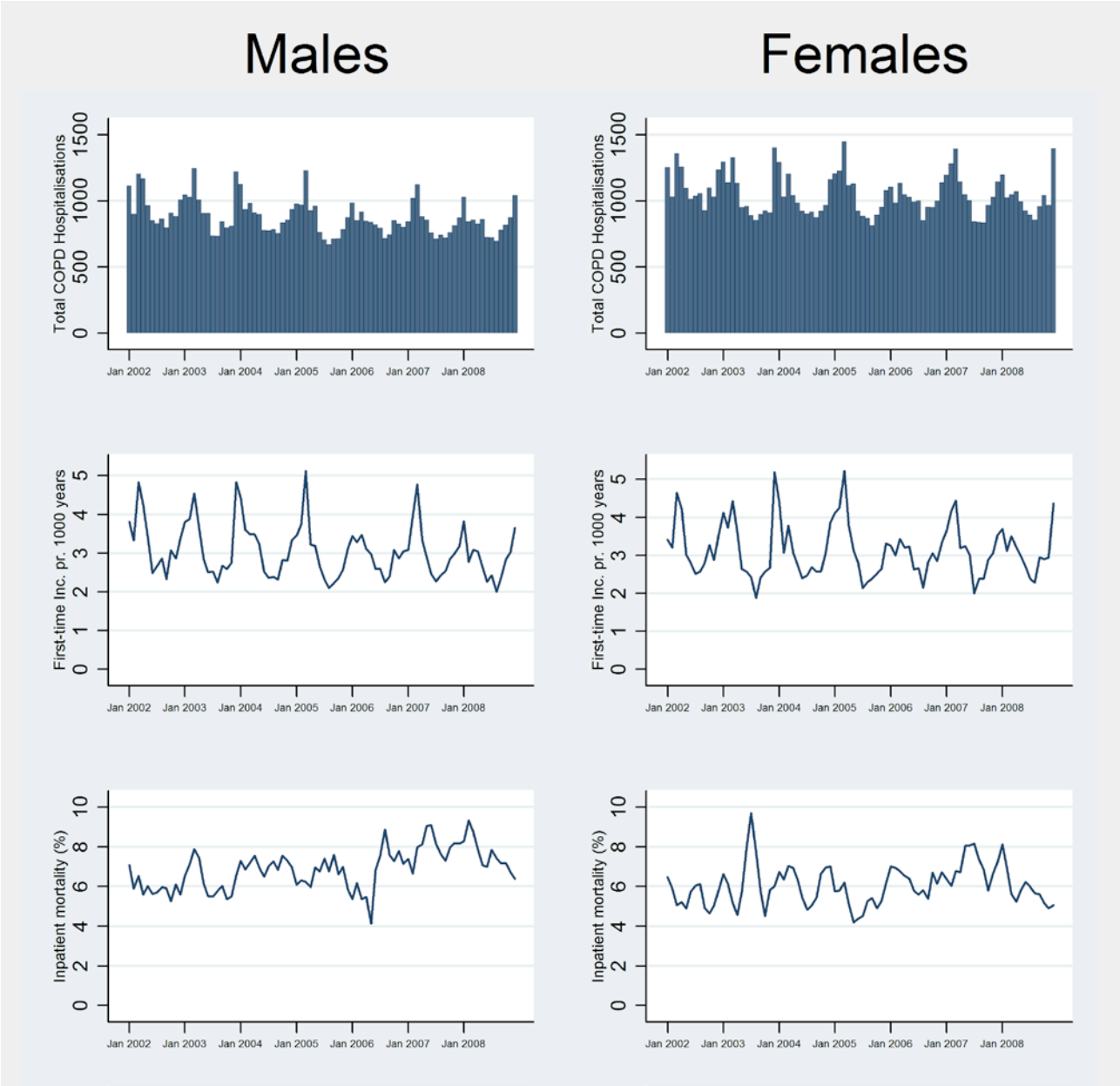

Figure 1: Total COPD hospitalisations, standardised incidence rate of first-time hospitalisations, and standardised inpatient mortality (running 3 month average). All standardisations are direct on the age distribution of the 2008 Danish population.

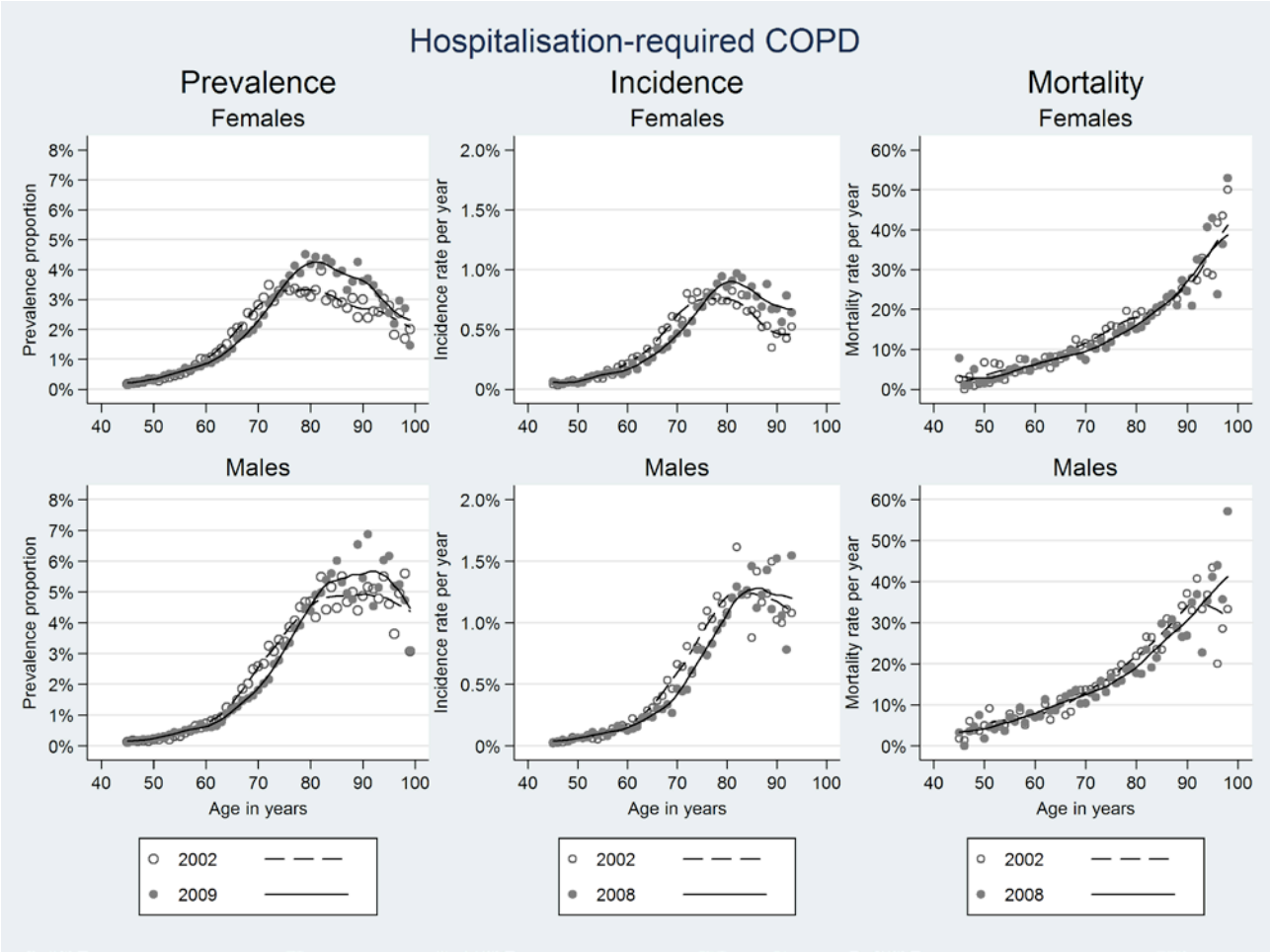

Figure 2: Age- and sex-specific prevalence, incidence, and mortality of hospitalisation-required COPD in the beginning and end of the study period.

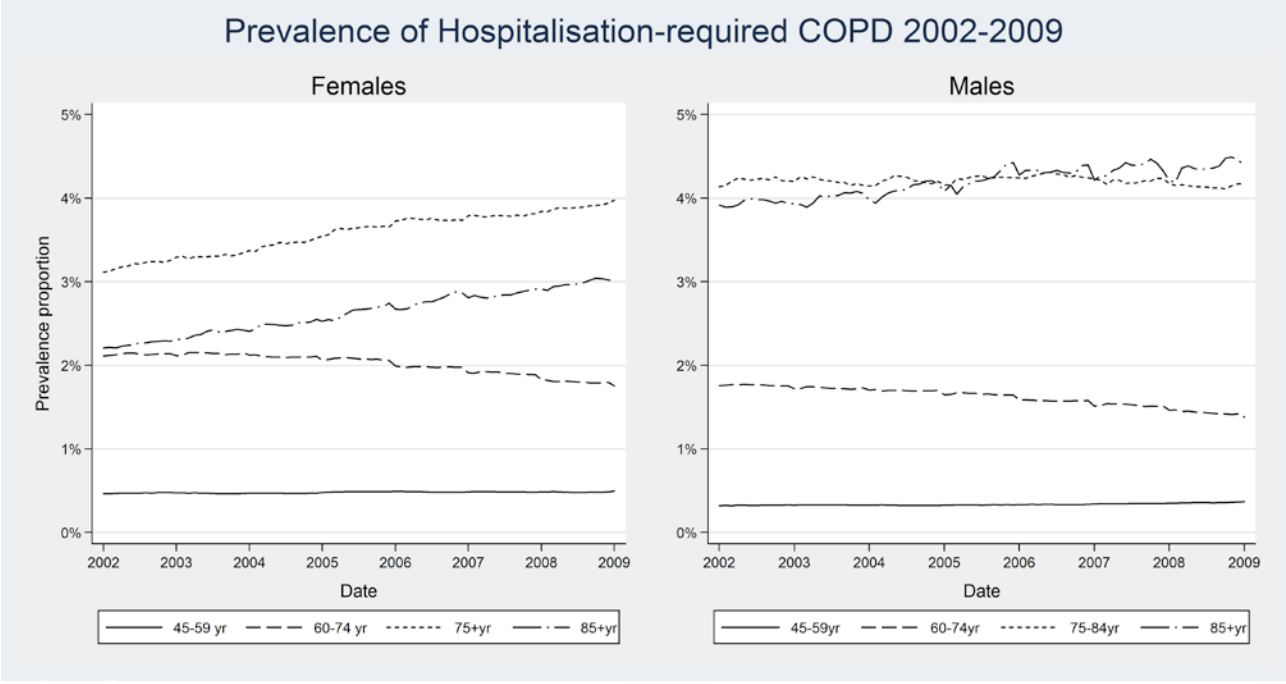

Figure 3: Monthly age- and sex-specific prevalence of hospitalisation required COPD 2002-2009.

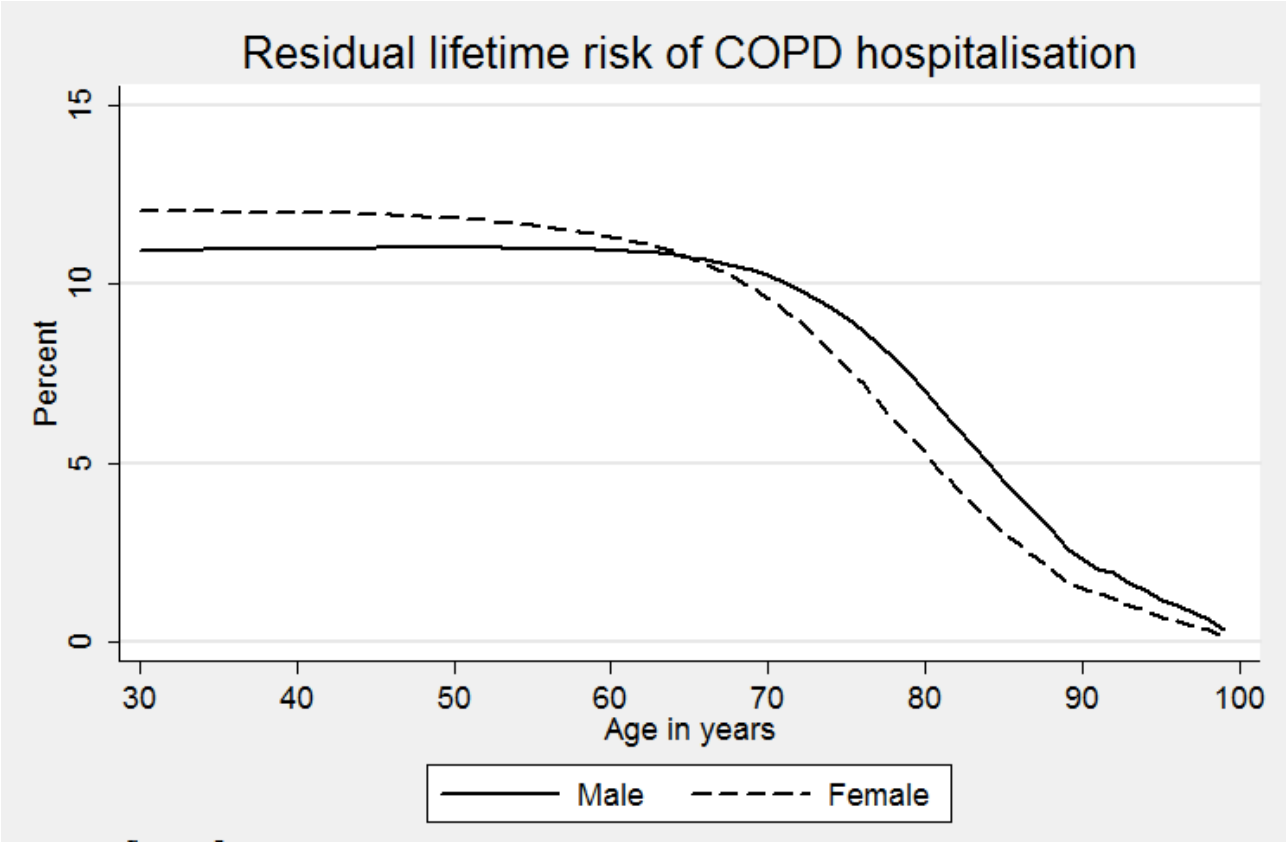

Figure 4: Residual lifetime risk of hospitalisation with COPD.

Table 1: Entry and exit of the population of Danes with HRCOPD 2002-2009

		2002	2003	2004	2005	2006	2007	2008	2009
Women 45-74 yrs	Prevalence 1 Jan	10,538	10,690	10,770	10,831	10,902	10,725	10,512	10,415
	New cases	+2185	+2121	+1992	+2110	+1860	+2012	+1940	
	Mortality *(%)*	-1146*(9)*	-1106*(9)*	-981*(8)*	-982*(8)*	-976*(8)*	-1068*(8)*	-944*(8)*	
	Migrations	-6	-9	0	-7	-3	-6	-3	
	Aged 45 - aged 75	-628	-629	-644	-675	-615	-688	-634	
	End of period	-253	-297	-306	-375	-443	-463	-456	
	Population 1 Jan	917,383	926,050	934,984	944,648	993,403	966,717	978,480	993,517
Women 75+ yrs	Prevalence 1 Jan	6834	7125	7363	7670	8001	8196	8394	8578
	New cases	+1505	+1525	+1525	+1620	+1621	+1734	+1751	
	Mortality *(%)*	-1700*(20)*	-1718*(20)*	-1647*(19)*	-1769*(19)*	-1804*(19)*	-1938*(19)*	-1957*(19)*	
	Migrations	-1	-1	-3	-3	-2	-1	-1	
	Aged 75	+695	+680	+688	+749	+687	+765	+704	
	End of period	-208	-248	-256	-266	-307	-362	-313	
	Population 1 Jan	239,365	237,968	237,296	236,843	236,625	236,033	235,525	235,357
Men 45-74 yrs	Prevalence 1 Jan	7879	7923	7932	7959	7940	7897	7876	7821
	New cases	+1788	+1804	+1699	+1706	+1685	+1725	+1681	
	Mortality*(%)*	-1028*(11)*	-1082*(11)*	-943*(10)*	-915*(9)*	-929*(10)*	-915*(10)*	-956*(10)*	
	Migrations	-3	-4	-6	-12	-2	-5	-8	
	Aged 45 - aged 75	-472	-509	-466	-539	-480	-484	-441	
	End of period	-241	-200	-257	-259	-317	-342	-331	
	Population 1 Jan	895,709	906,138	916,010	926,489	938,412	950,304	963,591	979,066
Men 75+ yrs	Prevalence 1 Jan	5680	5797	5826	5916	6099	6148	6220	6217
	New cases	+1471	+1447	+1428	+1408	+1399	+1567	+1420	
	Mortality *(%)*	-1734*(24)*	-1797*(25)*	-1680*(23)*	-1648*(23)*	-1671*(22)*	-1791*(23)*	-1694*(22)*	
	Migrations	-1	0	-2	-1	-2	-2	-2	
	Aged 75	+525	+543	+517	+595	+535	+538	+488	
	End of period	-144	-164	-173	-171	-212	-240	-215	
	Population 1 Jan	139,968	140,484	141,630	142,600	144,008	145,395	147,011	148,982

Mortality gives the number of deaths among the prevalent and incident cases in total and as percentage of the sum of

Table 2: First-time COPD hospitalisations in Denmark 2002 to 2008.

	2002			2008			Change 2002 to 2008	
	No. with new COPD	**Population at risk**	**IR per 1000 years**	**No. with new COPD**	**Population at risk**	**IR per 1000 years**	**$IRR_{2008/2002}$ age- & sex-adj.**	**IRR_{Annual} age- & sex-adj.**
Females aged								
45-59 years	547	554 604	1.0	500	542 811	0. 9	0.94(0.83-1.06)	0.99(0.97-1.00)
60-79 years	2314	443 831	5.2	2133	510 584	4.2	0.80(0.75-0.85)	0.97(0.96-0.97)
80+ years	829	140 690	5.9	1059	142 396	7.5	1.27(1.16-1.39)	1.04(1.03-1.05)
All ages	**3690**	**1 139 125**	**3.2 [Std]**	**3692**	**1 195 791**	**3.1**	**0.96(0.92-1.01)**	**0.99(0.99-1.00)**
Males aged								
45-59 years	441	564 963	0. 8	455	549 879	0. 8	1.06(0.93-1.21)	1.01(0.99-1.03)
60-79 years	2051	388 047	5.3	1779	472 420	3.8	0.71(0.67-0.76)	0.95(0.94-0.95)
80+ years	767	68 945	11.2	867	74 866	11.6	1.05(0.95-1.15)	1.02(1.00-1.03)
All ages	**3259**	**1 021 955**	**3.3 [Std]**	**3101**	**1 097 165**	**2.8**	**0.87(0.83-0.91)**	**0.98(0.97-0.99)**
Overall aged								
45-59 years	988	1 119 567	0. 9	955	1 092 690	0. 9	0.99(0.91-1.09)	1.00(0.99-1.01)
60-79 years	4365	831 878	5.3	3912	983 004	4.0	0.76(0.73-0.79)	0.96(0.95-0.96)
80+ years	1596	209 635	7.6	1926	217 262	8.9	1.16(1.09-1.24)	1.03(1.02-1.04)
All ages	**6949**	**2 161 080**	**3.3 [Std]**	**6793**	**2 292 956**	**3.0**	**0.92(0.89-0.95)**	**0.99(0.98-0.99)**

Analysed using Poisson regression. Age- & sex-adjusted when appropriate. 95% confidence intervals in parentheses.

Abbreviations: IR, Incidence Rate; $IRR_{2008/2002}$, IR ratio comparing 2008 with 2002; IRR_{annual}, IR ratio for the increase of one calendar year calculated using all annual data during 2002 to 2008; [Std] Standardised on the Danish 2008 population.

Table 3: Trends in first-time COPD hospitalisations in Denmark during 2002 to 2008.

	2002	2008	Age- and sex-adjusted logistic regression:		
No. first-time COPD hospitalisations	6949	6793			
No. receiving hospitals	70	58			
	% of cases	**% of cases**	**$OR_{2008/2002}$(CI95%)**	**OR_{annual}(CI95%)**	**P_{trend}**
Diagnosis code:					
J44 prim.	67.8	62.2	0.79(0.74-0.85)	0.97(0.96-0.98)	<0.001
J13-18 prim. + J44 sec.	15.5	21.2	1.45(1.33-1.58)	1.05(1.04-1.06)	<0.001
J96 prim. + J44 sec.	5.9	9.9	1.76(1.55-2.00)	1.10(1.09-1.12)	<0.001
J41-43 prim.	7.7	4.9	0.61(0.53-0.70)	0.91(0.89-0.93)	<0.001
J13-18 prim. + J41-43 sec.	2.6	1.3	0.49(0.38-0.63)	0.89(0.86-0.91)	<0.001
J96 prim. + J41-43 sec.	0.5	0.5	0.98(0.60-1.61)	1.02(0.96-1.08)	0.53
Male gender	46.9	45.6	0.95(0.89-1.02)	0.99(0.98-1.00)	0.17
One-year mortality	23.2	25.9	1.12(1.03 - 1.21)	1.02(1.01 - 1.03)	0.001
Inpatient mortality	5.9	7.0	1.16(1.01 - 1.34)	1.03(1.01 - 1.05)	0.002
Stay in intensive care unit	1.2	1.7	1.42 (1.07 - 1.88)	1.09(1.05 - 1.13)	<0.001
Department of internal medicine	96.0	96.0	0.97(0.82-1.15)	0.99(0.96-1.00)	0.23
Private hospital	0.01	0.09	-	-	-
Travel distance > 25 km	10.5	21.9	2.43(2.21-2.68)	1.16(1.15-1.18)	<0.001
COPD outpatient 1 year prior	9.4	11.1	1.25(1.12-1.40)	01.04(1.03-1.06)	<0.001
GP spirometry 1 year prior	14.6	17.6	1.31(1.20-1.44)	1.05(1.04-1.07)	<0.001
Prescriptions 1 year prior:					
Short-acting bronchodilators	81.3	58.2	0.60(0.56-0.64)	0.92(0.91-0.93)	<0.001
Long-acting beta2agonists	33.6	45.8	1.74(1.62-1.87)	1.10(1.09-1.11)	<0.001
Inhaled corticosteroids	49.2	54.5	1.26(1.17-1.34)	1.04(1.03-1.05)	<0.001
Tiotropium	4.0	27.2	9.57(8.39-10.93)	1.21(1.20-1.23)	<0.001
Oral corticosteroids	8.7	9.8	1.11(0.99-1.25)	1.04(1.02-1.05)	<0.001
			Age- and sex-adjusted linear regression:		
	Mean	Mean	2008-2002(CI95%)	Annual(CI95%)	P_{trend}
Age / years	71.6	72.2	0.66(0.26-1.05)	0.13(0.08-0.18)	<0.001
Length of stay/days	8.8	8.4	-0.43(-0.83 - -0.03)	-0.08(-0.13- -0.03)	0.003
No. prior all-cause hospitalisations	3.1	3.7	0.53(0.38 – 0.68)	0.09(0.07–0.11)	<0.001
Comorbidity (Charlson)	1.03	1.28	0.25(0.20 - 0.30)	0.04(0.03-0.05)	<0.001
Bed occupancy rate/%	99	102	2.5(2.0-3.1)	0.27(0.20–0.34)	<0.001
GP encounters 1 year prior:					
Consultations	7.4	9.1	1.82(1.53-2.11)	0.31(0.27-0.35)	<0.001
Telephone consultations	11.9	13.1	0.99(0.48-1.51)	0.16(0.10-0.22)	<0.001
Home visits daytime	1.26	1.06	-0.30(-0.39- -0.19)	-0.05(-0.06- -0.03)	<0.001
Home visits out-of-hours	0.72	0.72	-0.03(-0.06-0.00)	0.00(-0.01-0.00)	0.22

Abbreviations: OR, Odds Ratio; CI, confidence interval; P_{trend}, p-value of an annual trend throughout the period.

Table 4: Trends in the Danish prevalence of HRCOPD 2002 to 2009

	2002			2009			Change: 2002 to 2009	
	HRCOPD	**Population**	**PP**	**HRCOPD**	**Population**	**PP**	**POR $_{2009/2002}$**	**POR$_{annual}$**
Females								
45-59	2640	557,276	0.47%	2682	548,449	0.49%	1.04(0.99-1.10)	1.005(0.999-1.011)
60-74	7898	360,107	2.19%	7733	445,068	1.74%	0.80(0.77-0.82)	0.965(0.962-0.969)
75-84	5271	168,956	3.12%	6313	159,587	3.96%	1.28(1.24-1.33)	1.036(1.031-1.040)
85+	1563	70,409	2.22%	2265	75,770	2.99%	1.36(1.28-1.45)	1.047(1.039-1.054)
All ages	**17,372**	**1,156,748**	**1.51% ^{Std}**	**18,993**	**1,228,874**	**1.55%**	**1.04(1.02-1.06)**	**1.004(1.002-1.008)**
Males								
45-59	1862	566,848	0.33%	2020	554,915	0.36%	1.11(1.05-1.19)	1.013(1.006-1.020)
60-74	6017	328,861	1.83%	5801	424,151	1.37%	0.75(0.72-0.78)	0.959(0.955-0.963)
75-85	4568	111,388	4.10%	4802	116,296	4.13%	1.01(0.97-1.05)	1.001(0.997-1.006)
85+	1112	28,580	3.89%	1415	32,686	4.33%	1.12(1.03-1.21)	1.016(1.007-1.025)
All ages	**13,559**	**1,035,677**	**1.36% ^{Std}**	**14,038**	**1,128,048**	**1.24%**	**0.93(0.90-0.95)**	**0.989(0.986-991)**
Overall, y								
45-59	4502	1,124,124	0.40%	4702	1,103,364	0.43%	1.07(1.03-1.12)	1.008(1.004-1.013)
60-74	13,915	688,968	2.02%	13,534	869,219	1.56%	0.78(0.76-0.80)	0.963(0.960-0.965)
75-84	9839	280,344	3.51%	11,115	275,883	4.03%	1.15(1.12-1.19)	1.020(1.017-1.023)
85+	2675	98,989	2.70%	3680	108,456	3.39%	1.26(1.20-1.32)	1.035(1.029-1.040)
All ages	**30,931**	**2,192,425**	**1.44% ^{Std}**	**33,031**	**2,356,922**	**1.40%**	**0.99(0.98-1.01)**	**0.998(0.996-0.9996)**

Analysed using logistic regression. Age- & sex-adjusted when appropriate. 95% confidence intervals in parentheses. Abbreviations: HRCOPD, subjects with hospitalisation-required COPD; PP, Prevalence Proportion; POR, Prevalence Odds Ratio; CI, confidence interval; ^{Std} Standardised to the Danish 2009 population; ^{a} adjusted for age; ^{s} adjusted for sex; $_{2009/2002}$ comparing 2009 with 2002.

Table 5: Lifetime risk of COPD hospitalisation during 2002 – 2008

	Males		**Females**	
Period	**Lifetime risk/%**	**95% CI***	**Lifetime risk/%**	**95% CI***
2002	11.1	10.2-11.9	12.0	9.7-14.4
2003	11.1	10.3-11.9	11.9	10.5-13.4
2004	10.8	9.7-12.0	11.7	11.0-12.5
2005	10.9	9.5-12.3	12.4	10.7-14.0
2006	10.6	9.9-11.4	11.6	11.0-12.2
2007	11.4	10.4-12.4	12.4	11.4-13.5
2008	10.7	9.8-11.7	12.3	11.3-13.3
2002-2008	10.9	10.8-11.1	12.0	11.9-12.2

Abbreviations: CI*, Normal based bootstrap estimated confidence intervals.

Table 6: Lifetime risk of COPD hospitalisation at specific ages

	Males		Females	
Age	**Lifetime risk**	**95% CI***	**Lifetime risk**	**95% CI***
30	0.109	0.108-0.111	0.120	0.119-0.122
40	0.110	0.109-0.111	0.120	0.119-0.121
50	0.110	0.109-0.111	0.118	0.117-0.120
60	0.109	0.108-0.111	0.113	0.112-0.115
70	0.102	0.101-0.104	0.096	0.095-0.097
80	0.070	0.069-0.072	0.053	0.051-0.054
90	0.023	0.021-0.025	0.015	0.014-0.016

Abbreviations: CI*, Normal based bootstrap estimated confidence intervals.

Table 7: First-time COPD hospitalisations in Denmark 2002 characterised according to diagnosis codes:

COPD defining diagnosis:	**Chronic obstructive pulmonary diseases (J44)**			**Chronic bronchitis or Emphysema (J41-43)**		
Primary diagnosis:	**J44**	**Pneumonia (J13-18)**	**Resp. failure (J96)**	**J41-43**	**Pneumonia (J13-18)**	**Resp. failure (J96)**
[Age] years	71.2	73.2	71.3	71.2	74.3	71.1
Male gender %	46.1	51.1	40.9	47.2	52.7	65.6
Inpatient mortality %	4.1	8.6	16.3	5.1	7.1	40.6
One-year mortality %	21.4	27.6	32.1	21.1	22.5	56.3
Intensive care unit %	0.5	1.2	10.0	0.4	5.5	12.5
Department of internal medicine %	97.7	95.2	91.5	95.9	94.5	96.9
[Department Occupancy rate]	99	101	105	98	98	99
Travel distance > 25km %	10.7	10.0	8.8	11.7	12.1	6.3
[Charlson comorbidity index]	0.99	1.16	1.28	0.92	1.12	1.16
COPD outpatient 1 year %	9.7	7.2	15.1	8.5	5.5	6.3
Inhaled corticosteroids 1 year %	50.1	49.2	49.4	40.4	42.9	28.1
Long-acting beta2agonists 1 year %	35.4	31.3	32.3	25.8	27.5	31.3
Short-acting bronchodilators 1 year %	85.6	70.3	80.3	71.8	66.5	75
[No. GP consultations 1 year]	7.6	6.9	6.4	7.3	7.9	8.5
[No. GP telephone consultations 1 year]	12.0	12.0	11.0	12.2	11.6	12.3
[No. GP home visits daytime 1 year]	1.2	1.4	1.2	1.3	1.5	1.4
[No. GP home visits after hours 1 year]	0.7	0.8	0.8	0.8	0.7	0.7

Squared brackets indicate means. % indicates the proportion of cases in percent. Abbreviations: resp., respiratory; GP, general practitioner.

6 Discussion

6.1 Main findings

This study analysed data with 15 years of continuous and complete coverage of the entire population of Denmark. It showed that in 2009 1.36% of the Danish population above 45 years of age had been hospitalised with COPD. During the period from 2002 to 2009 this prevalence was roughly stable. Also, the lifetime risk of COPD hospitalisation was stable: For 30-year-olds, the study estimated that 12% of females and 11% of males will develop COPD to a degree requiring hospitalisation.

However, not all trends were stable. From 2002 to 2008 the total number of COPD hospitalisations in Denmark decreased along with the adjusted rate of first-time COPD hospitalisations. Furthermore, according to age and sex, rather dramatic changes were discovered: Both incidence and prevalence increased with age but only until a certain (peak) age, after which it decreased. Throughout the study period, for each increase of one calendar year, these peak ages for incidence and prevalence increased with just about one year (Figure X). Therefore, regarding both the prevalence and incidence of HRCOPD large decreases and increases (both about 20%) were observed in the age groups below and above the peak ages.

Regarding first-time COPD hospitalisations substantial increases were observed in the inpatient and one-year mortality, comorbidity, use of intensive care as well as other indicators of case severity. The receiving hospitals were reduced in numbers, the departments were increasingly overcrowded, and the average patient travel distance increased. In the year prior to COPD hospitalisation, more patients received the recommended pharmacotherapy, more patients had spirometry, and the patients had more encounters in general practice and outpatient hospital clinics.

6.2 Strengths and limitations

6.2.1 Size and completeness

The study covers all 5.4 million individuals in an entire nation for 15 years using the same disease classification, ICD-10. The unique Danish Civil Registration System provided exact age- and sex-specific counts of all subjects and deaths in the population. The use of virtually complete and prospectively collected data on all hospitalisations, deaths, and migrations largely eliminates the potential for selection bias. Also,

the wide spectrum of first-time hospitalisation characteristics is a major strength of the study and a rarity in register-based studies.

Characteristics of the Danish healthcare system further improved the completeness of the identified HRCOPD population and thus reduced the risk of selection bias. The Danish healthcare system is homogenous and access to COPD hospitalisation was equal and free of charge for all citizens throughout the period. Decisions to hospitalise were made by specialists in general medicine, and there was no intermediate option between hospitalisation and primary care treatment.

6.2.2 Data validity

The diagnoses obtained from the NPR were coded by the doctor responsible for the hospital discharge and validated in a 2008 nationwide study, which found a positive predictive value of 92% for COPD (10). As suggested in the validation paper (10), in order to minimise the influence of diagnostic drift, the codes J41-43 (chronic bronchitis and emphysema) were added to the COPD definition. As shown in Table 5, big differences were found between patients included by different sets of diagnoses, but hospitalisations coded with J41-43 did not particularly differ compared to J44 (COPD).

Despite the high specificity of the COPD diagnosis codes, misclassification remains a potential limitation of our study. No spirometry data were available to further validate the diagnosis. Hence, some hospitalisations may in error have been coded with COPD, but probably more COPD caused hospitalisations were miscoded with other diagnoses, mainly acute bronchitis, pneumonia, respiratory failure, or cardiac failure (10,118). This would lead to a general underestimation of the HRCOPD incidence, prevalence, and lifetime risk. Also, such underestimation might in part explain the decreasing incidence and prevalence at very high age. This would be the case if among all subjects hospitalised due to COPD exacerbation the very old subjects were more likely to be misdiagnosed. However, misclassification and diagnostic drift are not likely to have produced the opposing trends between age groups above and below 75 years of age.

Data from the Danish civil registration system (CRS) included civil registration number, sex, residence, and dates of birth, death, and migration. They are generally accepted to be of very high quality. First, information in CRS is used continuously by the administrative system in Denmark, which corrects errors whenever they are encountered. Second, high quality is ensured by the ongoing validation of information recorded. Third, all residents obtain a civil registration number certificate including their own

personal information so that potential errors can be corrected. Fourth, registration in CRS is required by law. Fifth, there is a positive public attitude towards registration in CRS. Sixth, the civil registration number includes easily accessible information on date of birth and sex of each individual, thus ensuring a good quality of the registration of sex and date of birth (113).

The Danish National Prescription Registry is based on reimbursement-driven record keeping and data are entered by use of automated bar codes. It is considered highly valid and almost complete (115). All the above-mentioned COPD drugs are available only by prescription and only in very rare cases handed out for free by doctors and hospitals. To be included in this study the drug needed to be prescribed by the doctor and redeemed by the patient. Sometimes the patient does not redeem a prescription. Thus, the study may underestimate the GP's intention to start COPD medication. Another limitation of using prescription data is the uncertainty as to whether a purchased drug is actually being used by the patient. Especially within the field of cardiovascular primary prevention non-compliance is substantial, and COPD medication is much more expensive that the ordinary antihypertensive drug. However, as opposed to patients prescribed with drugs for cardiovascular primary prevention, most COPD patients have symptoms and immediately feel the benefit of medication. Therefore, among COPD patients, non-compliance probably occurs less often.

The Primary Health Care Database exclusively provided service records. GPs are paid according to those records and thus underreporting is supposed to be minimal. The civil registration magnetic stripe card has to be presented at each primary care consultation. To some degree it prevents over-reporting of GP consultations.

6.2.3 First-time cases

The study exclusively identifies all first-time hospitalisations. The exclusion of recurrent cases prevents the study from being biased by oversampling of frequently hospitalised patients. In studies on consecutive patients over shorter periods such bias may lead to underestimates of severity and mortality, because high mortality selects less severe cases for frequent readmission. On the other hand, the COPD diagnosis may be less valid in patients only hospitalised once.

6.2.4 Lifetime risk method

Studies estimating the lifetime risk of various adverse events are often hampered by lack of clearly identified first-time events (80). However, in this study, overestimation of the lifetime risk due to misclassification of recurrent events as being incident is avoided by using individual look-back periods of 8 years to exclusively define first-time cases. The Canadian COPD study used only 5 years (83). Moreover, in this study, it was confirmed that further extension of the look-back period did not lower the lifetime risk estimates to any important degree.

Also, in this study, the mortality and incidence rates originated from the same population at risk. Other studies tend to use mortality rates of the general population or even a standard population. In case of COPD, especially in the old age groups, the prevalence of subjects with HRCOPD is high and their survival is substantially lower than that of the population without HRCOPD, i.e. still at risk (119,120). Hence, using the mortality of the general population without excluding subjects already prevalent with HRCOPD would have led to underestimation of survival and lifetime risk. On the other hand, when the specific mortality of each calendar year is used instead of the same standard mortality for all years (for instance that of 2008), it makes the lifetime risk trend estimate dependent on changes in both COPD hospitalisation rates and mortality rates of subjects never hospitalised with COPD. This approach is, however, preferred, since it is a central point in the concept of lifetime risk that decreasing age-specific incidence rates do not necessarily make the lifetime risk decrease, if at the same time more subjects survive into old age.

Regarding this study's ability to estimate the risk of future COPD hospitalisation, the main limitation lies in the dependence on time homogeneity of incidence and mortality rates. Future increases in life expectancy will increase the lifetime risk, while decreases in the HRCOPD incidence will decrease it. Life expectancy has been increasing steadily for more than two centuries (121) and improved treatment possibilities and lower airway exposure will probably make the incidence rate of HRCOPD decrease. The lifetime risk of COPD hospitalisation was estimated as the cumulative risk from the age of 30 years until the age of 104 years, which was the age of the oldest patient in the study. Hence, we assume time homogeneity of COPD hospitalisation rates and survival in the Danish population over the coming 74-year period. This assumption may seem rather crude. However, any prediction of future risks must be based on realistic "all other things being equal" assumptions (78, 80), and as COPD is a disease arising from long-term exposures, an overall measure such as lifetime risk is not likely to exhibit rapid changes in the near future. In other words, our

lifetime risk estimate for 80-year-olds is more reliable than that for 30-year-olds. The robustness of our estimate is also illustrated by its constancy over a seven-year period. The validity of the lifetime risk estimate is further discussed in the *Interpretation* section.

6.3 Generalisability

Optimal generalisability would imply that the findings of this study could be extrapolated to other populations and healthcare systems throughout the world. The incidence and prevalence of HRCOPD may vary among countries because of different frequencies of severe COPD exacerbations, and different severity thresholds for admission to hospital. In addition to the above, the lifetime risk of COPD hospitalisation varies among populations because of different life expectancies. International variation is more thoroughly discussed in the *Study results* section.

The lower age limits used in this study, 30 and 45 years respectively, restrict its generalisability. COPD hospitalisation is, however, extremely rare in people younger than 30. This means that the absolute numbers, e.g. that about 33 000 Danish subjects aged 45 years and above have HRCOPD, are almost not affected by lowering the age limit, while the relative numbers, e.g. the 1.36% prevalence proportion of HRCOPD among subjects aged 45 years and above, would be substantially decreased if the age limit was lowered.

Regarding the generalisability of this study it should be kept in mind that the reported mortality and other characteristics of first-time hospitalisation represent a pooled mass of hospitalisations, which occurred on different types of hospitals and departments. This means that all findings cannot necessarily be extrapolated to any specific department or type of departments and hospitals. Also, first-time COPD hospitalisations may be different from the day-to-day consecutive cases of which many are recurrent.

6.4 Study results

In the total Danish population, the study found a total of about 450 COPD hospitalisations per 100 000 person years. The total rate in the US is about 400/100 000 (39,66,68), and in Norway and Sweden, among subjects aged 40 years and above, rates of only about 550/100 000 have been reported (122). For decades the proportion of daily smokers has been higher in Denmark relative to other developed countries, especially

among women (108). This is most likely the cause of higher COPD hospitalisation rates in Denmark. However, the high completeness of Danish register data may also be a reason why the total rate of COPD hospitalisations in this study is higher than in studies from other countries.

The study confirms previous findings that the rate of COPD hospitalisations among females has been increasing relative to males and now exceeds that of males (66). It found a gradual but substantial decrease in the overall number of COPD hospitalisations. Combined with the findings of two prior Danish studies this shows that in Denmark, the rate of COPD hospitalisations increased rapidly during the 1990s and then rather suddenly started to decline (64,120). A similar pattern was observed in the US and is probably the case in many developed countries (39,66,68,74,120). Only in France the rates have continuously increased (63).

Characteristics of COPD hospitalisations found in this Danish study are quite similar to findings from most developed countries: As in the present study, cross-sectional studies from the UK and Belgium showed an increase in the average case severity of COPD hospitalised patients (123,124). Though the hospitalisation characteristics of this study differ somewhat from the Belgian findings, the inpatient mortality, age, gender, and length of stay is almost identical to the UK findings (3). A 2005 audit from Norway and Sweden showed the same length of stay as in our study, slightly older age of the patients, but an inpatient mortality of only 3.7% (122). Furthermore, both the levels of mortality and the excess mortality in males found in our study are in accordance with a large observational study from Canada (125). Finally, in this study as in other studies that include observations on the most elderly, the incidence of COPD increases with age until a certain age, above which it decreases (50,76). This finding will be discussed in the *Interpretation* section.

In the present study, among patients first-time hospitalised with COPD, both the inpatient and one-year all-cause mortality increased. In contrast, a prior study found that in Danish specialised pulmonary departments, during the same period, the same mortalities decreased (126). The latter was found among consecutive and not first-time COPD hospitalised patients, and the study was a repeated cross-section instead of a regular time-trend analysis. However, the inpatient and one-year mortality in Danish specialised departments of pulmonary medicine did probably decrease, and coexistence of both study results is possible, because the specialised departments of pulmonary medicine only receive a minority of all Danish COPD hospitalised patients. In a repeated cross-sectional study from Spain, the 3-year mortality after COPD hospitalisation decreased (127). This is not in conflict with the present findings in which the mortality of

patients prevalent with HRCOPD also decreased, indicating that although the one-year mortality increased, shortly thereafter decreasing mortality must be the case.

Trends in the rate of first-time COPD hospitalisations are rare. However, in a contemporary Danish study trends similar to those presented here were found. Although that study used the same registers and COPD definition codes as this study, it reported slightly lower rates. This was because it included subjects aged between 40 and 45 (higher risk time), because a longer look-back-period of 20-30 years including ICD-8 classified records was used, and because the study excluded hospitalisations of subjects with any prior secondary diagnosis of COPD instead of using the same COPD hospitalisation definition in this exclusion as in the inclusion periods (120). An identification of true first-time events that is both exclusive and exhaustive requires that the criteria used in the inclusion and look-back periods are the same. This approach was not adopted by the other study, likely because estimation of the absolute burden of COPD hospitalisations was not their major objective.

To our knowledge, neither the prevalence nor the lifetime risk of HRCOPD, let alone trends in those entities, has ever been reported in the previous literature. Hence, there are no prior studies to compare with. However, most COPD hospitalised patients have severe stages of the disease (16,47), and patients with severe COPD are frequently hospitalised. Therefore, the 1.36 overall prevalence of HRCOPD found in this study correlates well with the population surveys, which estimate a 0.8-2% prevalence of severe COPD in the Northern European adult population (43,46-48).

This study estimates that more than 10% Danish 30-year-olds will sometime later in life be hospitalised with COPD. Dutch and Canadian lifetime risk studies have estimated that 10-25% of the general population will develop COPD (50,76,83). COPD hospitalised patients probably represent a minority of all subjects who develop COPD (16,61). Hence, though the hospitalisation risk found in this study is lower than the general risk of the disease reported in other studies, it may reflect a higher burden of disease. The Dutch and Canadian studies may be expected to show lower burdens of disease, because they do not cover entire lifespans and because of more under-diagnosis of COPD in the general population than among hospitalised patients.

As stated above, compared to other developed countries, the rate of COPD hospitalisations is higher in Denmark. Hence, probably the lifetime risk of COPD hospitalisation in Denmark is higher too. However, though the mean life expectancy in Denmark is the same as in the US, it is shorter than in most European

countries (108). Shorter average lifespan means lower lifetime risk of chronic diseases, especially diseases that mainly occur in old age. Therefore, compared to Denmark, generally healthier populations may have higher lifetime risks of COPD hospitalisation.

6.5 Interpretation

During the period from 2002 to 2008, the total number of COPD hospitalisations as well as the adjusted rate of first-time COPD hospitalisations decreased. In the same period substantial increases were consistently found in several indicators of case severity, including mortality, comorbidity, use of intensive care unit, and prior use of oral corticosteroids. The combination of decreasing rates of hospitalisations and increasing severity of hospitalised patients indicates that the average severity threshold of hospital admission increased (128), so that less severe cases were more seldomly admitted to hospital. However, conclusions cannot be made as to whether this was because the GPs became better at treating exacerbations outside hospital and at selecting the correct patients for hospitalisation, or the development was forced by the contemporary reductions in the number of hospital beds.

Length of stay, which decreased, is usually an indicator of severity. However, in the study period the number of hospitals and beds were reduced, the patients had to travel further, the departments were increasingly overcrowded, and all other factors point in the direction of increasing severity. Therefore, the decreases in length of stay probably resulted from a combination of increased restrictions in the use of COPD hospital beds, shortening length of stay by lowering the threshold for discharge, and a possibly improved efficacy inside hospitals, which may have resulted in shorter lengths of stay regardless of the disease severity among the hospitalised COPD patients.

The combination of decreasing rate of first-time COPD hospitalisations and increasing severity might be explained by restriction in the use of the COPD diagnoses instead of restriction in hospitalisations of COPD patients. This is, however, unlikely, since increasing awareness of COPD and economic incentives to detect and diagnose COPD have characterised our study period (129). Furthermore, if COPD diagnosing was increasingly restricted to more severe cases, then the average length of stay should have increased. Instead it decreased, supporting the conclusion that it was in fact the use of COPD hospitalisation beds that was restricted, affecting the thresholds for both admission and discharge.

The decrease in Danish COPD hospitalisations probably transpired in J41-43 coded hospitalisations because during the study period Danish pulmonologists and the Danish National Board of Health increasingly recommended the use of J44 instead of J41-43 (10,114). Furthermore, in our study period the funding of Danish hospitals was increasingly based on the type and number of diagnoses, creating an incentive for more precise coding. A diagnostic drift driven by increased coding incentives would bias our findings towards underestimating the true decrease in COPD hospitalisations. In contrast, the increased coding incentives could explain some of the increase that we found in the average comorbidity index of COPD patients. However, during the study period, among patients first time hospitalised with COPD the average number of previous all-cause hospitalisations also increased, and we therefore believe that the overall comorbidity actually did increase. Furthermore, as an indicator of case severity the increase in mortality found in our study may be underestimated, because patients hospitalised late in the period most likely received an improved treatment, for instance by increased use of non-invasive positive pressure ventilation. The increase in this specific treatment may on the other hand partly explain the huge increase in the use of intensive care, because in most Danish hospitals this treatment required admission to an intensive care unit.

Importantly, the decreasing total number of COPD hospitalisations shows that the increased conduct of early discharge did not result in more readmissions.

While GPs treated increasingly severe COPD exacerbations outside hospital, the proportion of COPD patients medicated according to guidelines prior to their first hospitalisation improved substantially, perhaps explaining a reduction in the use of inhaled short-acting bronchodilators. Regarding the proportion of first-time COPD hospitalised patients who had had a spirometry in general practice, significant improvements were observed, though rates are still too low.

Healthcare systems all over the world aim to provide high quality benefits at the lowest cost, and treating diseases like COPD in primary care instead of hospitals has in the recent years been a major focus of this endeavour (130,131). In agreement with other studies (110,111), this study has demonstrated improvements in the COPD treatment in Danish primary healthcare. These improvements may have led to postponement of admission referrals and made it possible to reduce the number of hospital beds. Another interpretation of our findings is that the increased restrictions in the use of COPD hospital beds were induced by the reduction in hospital capacity, resulting in the increasingly overcrowded departments, which forced

general practice to treat increasingly severe cases. A combination may be the case. Whether the restrictions in the use of COPD hospital beds have affected the overall quality of care for COPD patients is largely unknown, but the Danish Registry of Causes of Death reports that the age- and sex-standardised death rates from pulmonary diseases in our study period remained constant (54).

In contrast to the gradual overall decrease in the COPD hospitalisation rate, the differences between the incidence and prevalence trends among subjects aged above and below 75 years are much more dramatic. Furthermore, it is interesting that the prevalence and incidence of HRCOPD increase with age only until a certain age, above which they decrease. These two effects cause the prevalence and incidence graphs to appear like rolling waves (Figure 2). These rolling waves are most likely mainly caused by differences in the total airway exposure throughout life in different birth cohorts.

The total Danish tobacco consumption per inhabitant increased rapidly after World War Two. It peaked between 1958 and 1977, after which it has significantly decreased (86). Hence, in their youth the birth cohort who turned 90 years in 2002 was not as exposed to tobacco as the birth cohort who turned 80 years the same year. Therefore, considering that most people start smoking before the age of 35 years it is likely that in 2002, despite the excess of life years, the 90-year-olds had a smaller cumulative tobacco exposure than the 80-years-olds. This probably explains why they had lower prevalence and incidence of HRCOPD. Furthermore, ageing of the 80-year-olds of 2002, with high levels of tobacco exposure, may be what caused the explosive increase in the incidence and prevalence of HRCOPD among 87-year-olds between 2002 and 2009 (Table 2, 4, and Figure 2). Likewise at the beginning of the wave, the decrease between 2002 and 2009 in HRCOPD among 60-75-year-olds may be due to increasingly lower exposure to the Danish tobacco epidemic from 1958 to 1977.

Previous studies have found that compared to birth cohorts before and after, Danish women born between 1915 and 1945 have an excess mortality, which is mainly from smoking-related diseases (132). This supports the fact that a wave of birth cohorts with high prevalence of COPD is rolling over Denmark.

In the past 99 years, besides from smoking, many other changing occupational and environmental airway exposures may also have contributed to causing the present birth cohort differences in incidence and prevalence of HRCOPD (34). In Denmark, during the period from 1930 to 1970 the economic sector of crafts and industries were the one employing most people (112). Furthermore, many of the harmful airway exposures associated with this booming third wave of Danish industrialisation many were later reduced by

prohibition or regulation. Hence, compared to the birth cohorts before and after, more subjects of the highly HRCOPD prevalent birth cohorts laboured in environments with harmful airway exposures.

Regarding the present trends in HRCOPD, as opposed to birth cohort effects, factors from within the study period probably also play a role. Above the age of about 85 years HRCOPD decreases with increasing age. This might be caused by a general reluctance to hospitalise the most elderly subjects. In contrast, a possible gradual lowering of the average threshold for admitting the most elderly and fragile subjects to hospital may have contributed to the HRCOPD increases in the elderly age groups observed during the study period (the right rolling of the wave). However, according to the above and probably as a result of major cutbacks in the number of Danish COPD hospital beds, the average admission severity threshold increased over the study period. Regardless of age, threshold changes due to cutbacks would most likely decrease the HRCOPD incidence. Hence, the large opposing age-specific trends are unlikely to be explained by changes in the severity threshold.

In the study period the treatment of COPD improved substantially in Denmark. Among Danish patients first-time hospitalised with COPD, tiotropium, long-acting-beta-2-agonists, and inhaled corticosteroids were increasingly used. Meanwhile, in Danish departments of respiratory medicine, the use of non-invasive ventilation (NPPV) gained currency. Evidence shows that these treatments reduce mortality and postpone the need for COPD hospitalisation (91,92,133). However, the treatment is given regardless of age and no treatment trials have shown large opposing effects on different age groups. Hence, regarding the observed changes improved treatment is unlikely to be a major explanatory factor. This consideration also applies to the possible influence of the known improvements in the treatment of COPD comorbidities. However, using this study design no further conclusions can be drawn as to the population impact of the improvements in neither the COPD-specific nor the COPD-comorbidity-related treatment.

The study found that the inpatient and one-year mortality of Danish patients first-time hospitalised with COPD increased, while mortality of all subjects prevalent with HRCOPD decreased. The overall increase in one-year mortality of subjects with incident HRCOPD was most likely caused by increasing case severity due to elevation of the average admission severity threshold. The coexistence of increasing one-year mortality of incident subjects and decreasing mortality of the prevalent subjects is only possible if survival increases above one year after the first COPD hospitalisation. This may be because one year after a COPD hospitalisation the mortality rate of HRCOPD subjects increasingly approaches the mortality rate of

the population without HRCOPD. We found that the latter decreased even more than the first, and this supports the above interpretation. Also, most likely the improved pharmacological treatment of stable COPD reduced the long-term mortality.

Reduced historical tobacco consumption may be the main reason why the survival among subjects without HRCOPD improved. Smoking causes most cases of HRCOPD. Therefore, regardless of improvements in their medical treatment, compared to subjects without HRCOPD, whose smoking prevalence decreased, the patients with HRCOPD had a smaller relative survival improvement.

Ageing effects represent a third way of interpreting the age-specific trend findings. Compared to the majority who die, people who survive into very old age may be genetically different in a way that renders them less susceptible to developing COPD and which causes the incidence of HRCOPD to decrease with very old age. This, however, does not explain the decreases among people below 75 years of age.

The study estimates that one out of ten 30-year-olds will be hospitalised with COPD. During the period from 2002 to 2008, in both sexes, the concurrent underlying mixture of increasing Danish over-all life expectancy (108) and decreasing incidence rates of first-time COPD hospitalisations kept the estimate constant. However, the study also shows recent substantial changes in exactly the factors, which in the lifetime risk assessment method are assumed to be constant. For example, regarding the most elderly, although having only a few years left to live, both their general survival and incidence of HRCOPD are increasing. Therefore, the study most likely underestimates their lifetime risk. Regarding the 30-year-olds, it is, however, unknown, whether increasing life expectancy or decreasing COPD incidence will be the stronger. Considering its limited long-term prediction ability, the presented lifetime risk is perhaps more valuable as a present benchmark, than as a predictor of the distant future. In a way that can relatively easy be compared across time, countries, and diseases it expresses the burden of HRCOPD in the Danish population of today.

For further interpretation of the study results it should be kept in mind that during the study period an unknown number of Danish subjects will likely have developed fatal COPD although never admitted to hospital for this. This number is difficult to assess using register data, mainly because comorbidity related to COPD is often recorded as the only cause of death (62).

7 Conclusion

If current age- and sex-specific mortality and COPD hospitalisation rates remain constant, more than 10% of all 30-year-old Danes will at some point be hospitalised with COPD. During the study period from 2002 to 2009, trends have, however, been far from constant. The incidence of first-time COPD hospitalisations has decreased along with the number of beds and receiving hospitals. Meanwhile the severity of cases increased. Hence, the average severity threshold for COPD hospitalisation increased, so that increasingly severe COPD exacerbations remained in primary care treatment, which both increased and improved. More important to the COPD trends in Denmark, the Danish population seems to be on top of a wave of birth cohorts with high prevalence of COPD. Cumulated, most likely these cohorts have had more exposure to both smoking and occupational respiratory hazards than the cohorts born before and after. With their passing a substantial decrease in the burden of COPD in Denmark will occur

8 Perspectives

Although only analysing the seven-year period from 2002 to 2009, the study found unexpectedly powerful trends as well as strong indications of influencing factors. Considering the high mortality and the severely reduced quality of life among patients with HRCOPD, the study confirms that COPD is among the most important public health problems.

The study found that COPD hospitalisations have become increasingly restricted to more severe cases. Therefore, each COPD bed day most likely demands more resources. Also, and perhaps more obviously, this development increases the workload in general practice. Since the increases in the admission severity threshold seem to follow reductions in the number of hospitals and beds for internal medicine the development may be the same for many diseases other than COPD. The funders and budget-planners for both the hospital departments and general practice should recognise this development. Also, future research and interpretations of hospital statistics should be aware of the potentially large volatility of the admission severity threshold.

The incidence and prevalence of HRCOPD peak in the birth cohorts from around 1930. Those were the subjects who had most exposure to the post World War Two smoking epidemic as well as the harmful gasses and particles of the third industrial revolution. The causal relation is without doubt. Thus, according

to this study, because of the historical decline in tobacco smoking and reduced occupational airway exposure, an overwhelming number of Danish lives are now saved from the suffering and death of COPD. Unfortunately, in Denmark and many countries all over the world smoking prevalence is still considerable. The process towards a tobacco-free world should be encouraged in any way. The study shows that a decrease in COPD did not occur until about 50 years after reductions in harmful airway exposures had begun. However, the indicated COPD-decreasing effect of these reductions was substantial. Thus, it should be kept in mind that when evaluating present initiatives, the effects should not be expected to take place within the first decades. The study predicts that in the coming decades a substantial decrease in the burden of COPD will occur. This decrease is demonstrated to be the result of birth cohort effects. Thus, without careful consideration, despite the growing evidence of the beneficial effects of treatment, the coming decrease in the burden of COPD should not be interpreted as a result of any sort of present healthcare initiatives.

For many years, compared to cancer and cardiovascular diseases, the attitude towards COPD has been different. Though the diseases are comparable as to frequency, lethality, and the degree of suffering, COPD has received much lesser attention and fewer resources. The reason for this inequality is probably that as opposed to the two other major diseases COPD neither occurs suddenly nor to young previously healthy persons. Also, COPD's association with smoking makes some people consider it to be self-inflicted. Besides from showing the large mortality rate among patients with HRCOPD and the indications that most of them developed the disease because of events in their youth some 50 years ago, this study provides a lifetime risk estimate that applies to young persons and can easily be communicated to the lay public and health politicians. Hopefully results like these can create attitudes changes and make preventive actions take place so that this prophecy will not come true.

The study suggests that improved management of patients with COPD in general practice is associated with the decline in COPD hospitalisations. However, it is unclear what GP features are associated with COPD hospitalisation prevention. Optimisation of GP prescribing patterns for COPD and its comorbidities, as well as the frequency of consultations, home visits, and tests such as spirometry, blood samples, chest X-rays, and electrocardiograms are all expected to facilitate improvement in the prognosis and wellbeing of the patients. Further research should try to discover which factors actually have an effect on COPD hospitalisation rates.

The cost savings associated with transferring severe COPD exacerbation from hospital to primary care indicate an obvious success. However, we do not know whether the patients are satisfied with this development. Also, only vague indications show that the transfer has been safe. Future research should focus on the possible risks of such transfers of tasks within healthcare systems.

9 Summary

This PhD thesis was performed during my employment at the Research Unit of General Practice in Odense, University of Southern Denmark. It comprises an overview of three papers, all published or submitted for publication in international peer-reviewed scientific journals.

Background: In industrialised countries exacerbation of chronic obstructive pulmonary disease (COPD) is among the most common causes of admission to hospital. In Denmark, during the period from 1991 to 2001 the number of COPD hospitalisations more than doubled. Many COPD hospitalisations are readmissions, and the mortality of the patients is high. Therefore changes in the total number of COPD hospitalisations do not necessarily represent changes in the number of patients. Furthermore, compared to the intensity of research on the causes of COPD in individuals, COPD causes on the societal level are sparsely investigated.

Aims:

- To investigate trends in first-time hospitalisations with chronic obstructive pulmonary disease (COPD) in a publicly financed healthcare system during the period from 2002 to 2008 with respect to incidence, outcome and characteristics of hospitalisations, departments, and patients *(Study I)*.
- To investigate age- and sex-specific trends in Denmark from 2002 to 2009 in the prevalence of COPD that has required hospitalisation *(Study II)*.
- To estimate the lifetime risk of hospitalisation with COPD in Denmark *(Study III)*.

Methods: By use of national registers a cohort study covering the entire Danish population from 1994 to 2009 was conducted. COPD hospitalisations were considered first-time (incident) if the patient had no COPD hospitalisations in the previous 8 years. Likewise, patients were considered prevalent with COPD that has required hospitalisation from the first-time COPD hospitalisation until either death or the end of an individual 8-year period with no COPD hospitalisations. Trends regarding incidence, mortality and characteristics of first-time hospitalised patients and their hospitalisations were analysed. With a special focus on birth cohort effects, the age- and sex-specific trends in the incidence and prevalence of COPD that has required hospitalisation were analysed. Finally, assuming that each year's age- and sex-specific mortality and COPD hospitalisation rates were to remain constant, the annual sex-specific lifetime risk of COPD hospitalisation was calculated.

Results: *Study I:* Denmark has yearly about 7000 first-time hospitalisations with COPD. During 2002 to 2008 the total number of Danish COPD hospitalisations decreased from 460 to 410 per 100 000 person years. Furthermore, the age- and sex-specific incidence rate of first-time COPD hospitalisations decreased by 8.2% (CI 5.0-11.2%), while the inpatient and one-year mortality increased by 16 and 12%, respectively. Concurrently, significant age- and sex-adjusted increases were found in the use of intensive care, comorbidity, patient travel distance, bed occupancy rate of the receiving department, prior use of oral and inhaled corticosteroids, use of outpatient clinics and encounters in general practice, while length of stay and number of receiving hospitals decreased. *Study II:* In 2009, about 34 000 Danes had been hospitalised with COPD. During the period from 2002 to 2008 among subjects aged 75 years or less, the incidence and prevalence of COPD that required hospitalisation decreased about 20%. In contrast, among subjects above 75 years of age increases of about 20% were found. *Study III:* For 30-year-old Danes the lifetime risk of hospitalisation with COPD is 12.0% (CI 11.9-12.2%) for women and 10.9 % (CI 10.8-11.1%) for

men. During the period from 2002 to 2008 the risk was roughly constant in both sexes.

Conclusion: If current age- and sex-specific mortality and COPD hospitalisation rates remain constant, more than 10% of all 30-year-old Danes will at some point be hospitalised with COPD. However, recent trends have been far from constant. The incidence of first-time COPD hospitalisations has decreased along with the number of beds and receiving hospitals. Meanwhile the severity of cases increased. Hence, the severity threshold for COPD hospitalisation increased, so that increasingly severe COPD exacerbations remained in primary care treatment. More important to the COPD trends in the Denmark, the Danish population seems to be on top of a wave of birth cohorts with high prevalence of COPD. Cumulated, most likely these cohorts have had more exposure to both smoking and occupational respiratory hazards than the cohorts born before and after. With their passing a substantial decrease in the burden of COPD in Denmark will occur.

10 Dansk resumé (Summary in Danish)

Denne ph.d.-afhandling er udført under min ansættelse ved Forskningsenheden for Almen Praksis i Odense, Syddansk Universitet. Den består af en oversigt samt tre artikler, der alle er offentliggjort eller indsendt til offentliggørelse i internationale peer-reviewede videnskabelige tidsskrifter.

Baggrund: I industrialiserede lande er exacerbation af kronisk obstruktiv lungesygdom (KOL) blandt de hyppigste årsager til hospitalsindlæggelse. Fra 1991 til 2001 blev antallet af KOL-indlæggelser i Danmark mere end fordoblet. Mange KOL-indlæggelser er genindlæggelser, og dødeligheden er høj. Derfor afspejler udviklingen i antallet af indlæggelser ikke nødvendigvis udviklingen i antallet af sygdomsramte. Endvidere har udviklingen i viden om årsager til KOL på samfundsniveau ikke fulgt med den tilsvarende viden på individniveau.

Formål: Vedrørende Danmark fra 2002 til 2009

- at analysere udviklingen i førstegangsindlæggelser for KOL med hensyn til incidens, mortalitet og karakteristika for patienter, indlæggelser og forløb (Studie I),
- at analysere den køns- og aldersspecifikke udvikling i prævalensen af indlæggelseskrævende KOL (Studie II), og
- at analysere udviklingen i livstidsrisikoen for KOL-indlæggelse (Studie III)

Metode: Gennem nationale registre udførtes et kohortestudie af hele den danske befolkning fra 1994 til 2009. Ud fra en 8-års run-in periode blev førstegangsindlæggelser for KOL identificeret, og udviklingen med hensyn til incidens, dødelighed, samt karakteristika for patient, indlæggelser og forløb blev analyseret. Den køns- og aldersspecifikke udvikling i incidens og prævalens af indlæggelseskrævende KOL blev analyseret. Endelig blev livstidsrisikoen for KOL-indlæggelse estimeret ud fra køns- og aldersspecifikke incidensrater for førstegangsindlæggelse for KOL og mortalitetsrater for befolkningen uden KOL-indlæggelse.

Resultater: *Studie I:* Danmark har årligt knap 7.000 førstegangsindlæggelser for KOL. Det totale antal KOL-indlæggelser i Danmark faldt fra år 2002 til 2008. Endvidere faldt den køns- og aldersjusterede incidensrate for førstegangsindlæggelser med 8,2% (CI 5,0-11,2%), mens dødeligheden under indlæggelse og inden for 1 år steg med henholdsvis 16 og 12%. Blandt førstegangsindlæggelser fandtes endvidere signifikante stigninger i: forbrug af intensiv terapi, komorbiditet, afstand til sygehus, afdelingsbelægningskvotient, forbrug af peroral og inhaleret kortikosteroid og kontakter i lungeambulatorier og almen praksis, mens indlæggelsestiden og antallet af modtagende sygehuse faldt. *Studie II:* Omkring 34.000 danskere har været indlagt for KOL. Blandt danskere under 75 år faldt incidensen og prævalensen af indlæggelseskrævende KOL kraftigt, mens den steg lige så kraftigt for dem over 75 år. *Studie III:* Livstidsrisikoen for, at en 30-

årig dansker vil blive indlagt for KOL, er 12,0 % for kvinder (CI 11,9-12,2) og 10,9 % for mænd (CI 10,8-11,1). Gennem perioden var risikoen stabil for begge køn.

Konklusion: Med status quo vil mere end 10% af alle 30-årige danskere senere i livet blive indlagt for KOL. Imidlertid har den seneste udvikling været langt fra stabil. Antallet af førstegangsindlagte faldt, sammen med antallet af sengepladser. Samtidig steg mortalitet, komorbiditet, ressourceforbrug, medicinsk behandling og antallet af kontakter i almen praksis og lungeambulatorier betydeligt. Dette viser, at tærsklen for indlæggelse øgedes, så tiltagende alvorlige KOL-exacerbationer blev behandlet i almen praksis. Mere væsentligt for samfundsudviklingen med hensyn til KOL er dog, at Danmark synes at befinde sig på toppen af en bølge af fødselskohorter med særlig høj prævalens af KOL. Dette skyldes formentlig den høje eksposition for rygning og andre luftvejsirritanter under industrialiseringsbølgen i perioden efter anden verdenskrig.

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12 Papers

I **All Danish first-time COPD hospitalisations 2002 – 2008: Incidence, outcome, patients, and care.** Lykkegaard J, Søndergaard J, Kragstrup J, Davidsen JR, Knudsen T, Andersen M. *Respir Med* 2012 Apr;106(4):549-56.

II **On the crest of a wave: Danish prevalence of hospitalisation-required COPD 2002 - 2009.** Lykkegaard J, Davidsen JR, Andersen M, Paulsen MS, Søndergaard J. *Respir Med* June 2012 [E-pub ahead of print] DOI: 10.1016/j.rmed.2012.06.004

III **Trends in the lifetime risk of hospitalisation with chronic obstructive pulmonary disease.** Lykkegaard J, Christensen RD, Davidsen JR, Støvring H, Andersen M, Søndergaard J. – *Submitted paper*